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THE SUPERIOR MESENTERIC ARTERY SYNDROME

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THE SUPERIOR mesenteric artery syndrome is an unusual form of high intestinal obstruction. It was first described by Rokitansky about a century ago. Various methods of operative and nonoperative treatment have been discussed in the literature during the past 50 years. Because this condition is sometimes neither recognized promptly nor treated properly, this report is presented of the experiences with the operative treatment of such cases during the past 6 years at the Indiana University Medical Center and the associated Veterans Administration Hospital. The nonoperative management of such cases will also be discussed briefly.

MATERIAL

Altogether 18 patients have been treated surgically (Tables I and II). The majority were young adults, though 6 were 51 or more years old and 5 were 61 or more years of age (Table III). Ten of the 18 were males, 4 with acute and 6 with chronic disease. Of the 8 females, 3 had disease of the acute type and 5, chronic. Four of the male patients, however, were from the Veterans Hospital where few female patients are admitted. Six of those treated at the Medical Center were males and 8 females.

Seven cases were of the acute type. There was no previous history of gastrointestinal complaints; all patients had been confined to bed because of illness, injury, or surgical procedure. Most of the patients had been in bed for weeks or months. One 81 year old female, however, began to vomit on the fifth postoperative day after resection of an abdominal aortic aneurysm. She failed to respond to a brief trial of medical management and was treated surgically. Three of the remaining 6 patients were bedridden because of cast or traction immobilization. The other 3 were confined to bed because of poliomyelitis, chronic mental disorder, and debilitating systemic disease. In all of them nausea developed with vomiting of bile-stained material, and usually there was epigastric fullness or discomfort. In some, epigastric distention was evident. In others whose upper gastrointestinal tracts were decompressed by emesis there was little to be detected on physical examination. Roentgenologic studies were usually diagnostic. Plain roentgenograms of the abdomen ordinarily revealed gaseous distention of the stomach and duodenum with little or no gas

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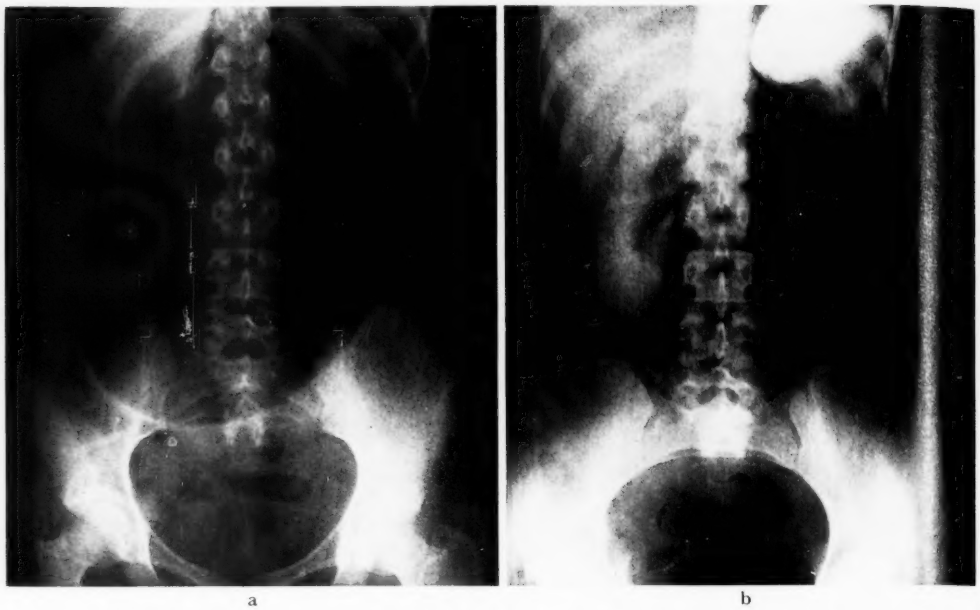

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FIG. 1. a, Plain roentgenogram of patient 4, Table I, illustrating gaseous distention of stomach and duodenum and lack of gas distally. b, Roentgenogram with water-soluble contrast medium showing classic superior mesenteric artery obstruction of duodenum.

in the more distal small intestine and colon (Fig. 1a). When the stomach and duodenum were adequately decompressed or contained fluid without gas, the condition could not be readily suspected from ordinary roentgenologic examination. Study of the upper gastrointestinal tract with contrast material verified the diagnosis. The stomach and duodenum were large and the pylorus patulous. The obstruction was delineated as a straight line cutoff just about at the lateral border of the right psoas shadow in the region of the junction of the second and third portions of the duodenum (Fig. 1b). Sometimes positioning of the patient in the left lateral or prone position allowed some of the contrast medium to pass beyond the point of obstruction.

In 1 case, plain roentgenograms of the abdomen revealed air in the hepatic portal venous system (Fig. 2). At operation, air was visible in the mesenteric veins, and this observation was confirmed also on postmortem examination. Just how air entered the portal venous system is a matter of conjecture. There was tremendous distention of the stomach and duodenum in this 19 year old mentally defective patient, and the intraluminal pressure must have been great. The patient had been given 0.3 milligram of prostigmine before admission to the hospital. This may have increased the pressure in the distended viscera. As far as we know this clinical entity has not been reported before.

There were 11 patients with the chronic or subacute type of disease. They all had intermittent abdominal pain or postprandial epigastric fullness. All but 2 had intermittent nausea and vomiting. The vomitus was bile-stained and usually contained recently ingested food. Some patients noted relief of distress in the prone or genupectoral position. None of the patients noted acholic stools. In 3, gastric analysis was performed. The findings were either negative, or there was no free acid and a low total acid. Complaints had been present for months or years in all except 2 patients. One was a 75 year

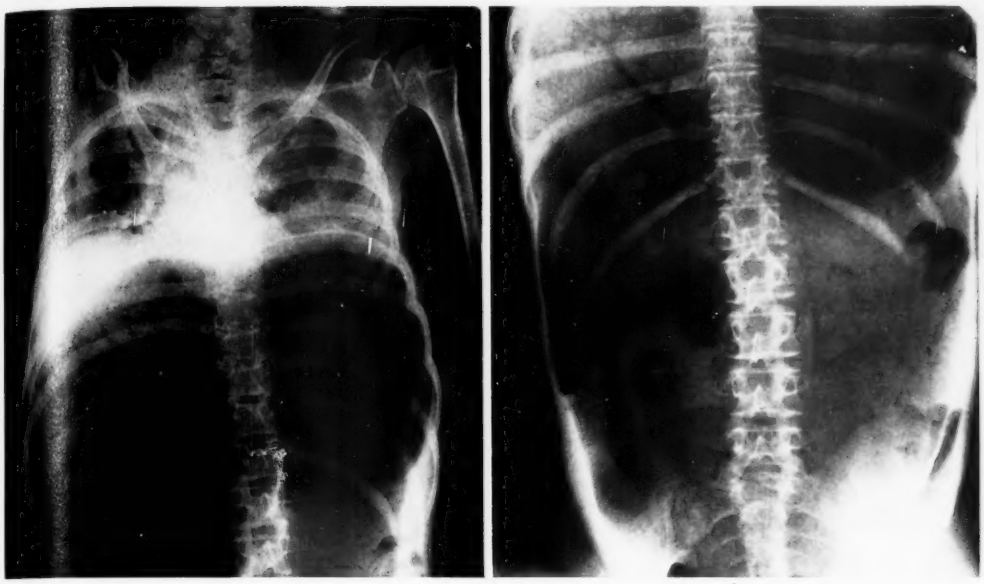

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FIG. 2. a, b, Plain roentgenograms of patient 2, Table I, illustrating elevation of diaphragms by greatly distended stomach and air in portal venous system.

old female whose abdominal pain, nausea, and vomiting was only of 1 week's duration, and the other a 21 year old student nurse with symptoms of 5 days' duration. All the patients were ambulatory, and all of them except 1 were thin or malnourished. The 21 year old student nurse was well nourished but because of hypertension had voluntarily lost 20 pounds by dieting in less than 2 months. She had a classic superior mesenteric artery syndrome which did not respond to a trial of medical management, but improved promptly after duodenojejunostomy. Three patients had associated, nonspecific hypertrophy of retroperitoneal lymph nodes; 2, enlarged lymph nodes of a neoplastic nature, and 1 a retroperitoneal hematoma. Physical and roentgenologic findings were similar to those observed in the acute cases. One, a 63 year old woman, who was admitted because during an operation performed elsewhere the surgeon thought he identified an aortic aneurysm, had normal upper gastrointestinal roentgenologic findings and no evidence of an aneurysm. In view of her severe symptoms and 50 pound weight loss an exploratory laparotomy was performed, and a classic superior mesenteric artery syndrome was found. A duodenojejunostomy was performed, and the patient had an uneventful recovery but is regaining weight very slowly. In view of the negative preoperative studies and the operative findings of marked distention of the stomach and duodenum down to the ligament of Treitz with collapse of the intestine distally, it was believed that she must have had intermittent, recurring superior mesenteric artery obstruction. In 1 patient who had cholecystograms, the dye was visualized in the stomach and duodenum, and in another the gallbladder was still opacified when a roentgenogram was made 3 days after the ingestion of the dye.

Because of failure of medical management to relieve symptoms, all 18 patients were treated by operation. One patient mentioned before as having roentgenologic evidence of a previous portal pneumovenogram appeared moribund at the time of

TABLE I.—DATA CONCERNING PATIENTS TREATED OPERATIVELY FOR ACUTE SUPERIOR MESENTERIC ARTERY SYNDROME

No. *Age, yrs.* *Sex*	*Nutrition*	*Associated disease*	*Signs and symptoms*	*Roentgenology*	*Duodeno-jejunos-tomy*	*Comments*
1 8 M	Cachectic	Undiagnosed myopathy	Abdominal pain, nausea and vomiting —16 days	Gastric and duodenal retention. Dilated duodenum	Yes	Duodenojejunostomy worked well. Expired a month after operation from pulmonary fibrosis and bronchopneumonia
2 19 F	Emaciated	Mentally defective	Tympanites. 0.3 mgm. prostigmine prior to transfer	Gastric and duodenal distention causing marked diaphragmatic elevation. No gas beyond duodenum. Air in portal venous system	No	Expired at operation. Air in hepatic portal vein and radicals at operation and postmortem
3 20 M	30 lb. weight loss	Fracture of acetabulum and femur dislocation treated by traction and cast	Vomiting first day after body cast applied. (Traction for prior month.) Severe electrolyte disturbance. Shock and azotemia	Gastric and duodenal dilatation with patulous pylorous and obstruction at third portion of duodenum. Marked duodenal churning and reverse peristalsis at fluoroscopy	Yes	Recovered
4 20 F	40 lb. weight loss	Poliomyelitis. Supine 3 months; in bed and respirator	Nausea and vomiting intermittently 2½ months, acutely 4 days	Gastric and duodenal dilatation. Obstruction third portion of duodenum	Yes	Recovered
5 25 M	Thin	Traumatic arthritis of hip. Treated with hip spica for 2½ months	Nausea and vomiting intermittently 5 wks. Severe electrolyte imbalance	Gastric and duodenal dilatation and retention of barium for 5+ hours	Yes	Recovered
6 67 M	Emaciated	Schizophrenia; hip spica for fractured femur 10 weeks	Vomiting and large amount of gastric suction 4 days	Gastric and duodenal dilatation and retention of barium for 7 hours	Yes	Recovered
7 81 F	Moderately well nourished	Resection of abdominal aortic aneurysm	Vomiting 5th postoperative day. Distended and tympanitic	Gastric and duodenal dilatation. Obstruction of duodenum at third portion. Churning of duodenal contents at fluoroscopy	Yes	Recovered

admission and expired shortly after the abdominal incision was made. The others were treated by side-to-side anastomosis of the jejunum to the dilated duodenum. The anastomosis was performed by bringing the jejunum up to the duodenum through an incision in the mesocolon to the right of the middle colic artery. After completion of the anastomosis the incision in the mesocolon was sutured to the duodenum about the anastomotic site. Three patients, though relieved of symptoms, died of intercurrent or underlying disease. One patient expired a month after operation of advanced pulmonary fibrosis and bronchopneumonia, and 2 died of cancer 11 days and 7 weeks postoperatively. The remaining 14 patients survived and had complete relief of their symptoms.

DISCUSSION

Survey of these operatively treated patients illustrates the typical features of this disease. It takes two different forms. The acute form occurs without a previous history of gastrointestinal symptoms and is usually precipitated by a somewhat prolonged period of immobilization necessitated by unrelated disease, injury, or operation. It is especially likely to occur when the patient is forced to lie supine most of the time. The patients become nauseated, complain of abdominal distress and distention, and vomit. The subacute or chronic form tends to occur in tall, slender, or undernourished individuals. They complain periodically of flatulence, postprandial epigastric fullness, and vomiting of bile-stained material usually containing recently eaten

TABLE II.—DATA CONCERNING PATIENTS TREATED OPERATIVELY FOR SUBACUTE SUPERIOR MESENTERY ARTERY SYNDROME

No. *Age, yrs* *Sex*	*Nutrition*	*Associated disease*	*Signs and Symptoms, laboratory data*	*Roentgenology*	*Duodeno-jejunos-tomy*	*Contributing factor*	*Comments*
1 11 M	Thin	Mesenteric lymphad-enopathy	Nausea, vomiting, and abdominal pain	Duodenal obstruction 3rd portion	Yes	Mesenteric lymphad-enopathy	Recovered
2 16 M	Emaciated	Malignant lymphoma	Abdominal pain 5 weeks. Vomiting 2 days	Gastric and duodenal dilatation and retention. Obstruction at third portion duodenum	Yes	Retroper-itoneal malignant lymphoma	Anastomosis functioned well. Expired 7th postoperative week from lymphoma
3 18 M	Thin	Gastrojejunos-tomy for duodenal obstruction	Abdominal pain, postprandial fullness 2½ months, unrelieved by gastrojejunostomy	Gastric and duodenal dilatation and retention 5½ hrs. Gastrojejunostomy functioned with patient prone	Yes	Retroper-itoneal hematoma	Recovered. Gastrojejunostomy taken down when duodenojejunostomy was performed
4 21 F	Moderately well nourished	20 lb. weight loss in 2 mos. due to hypertension	Epigastric pain, nausea and vomiting postprandial, 5 days	Dilatation of duodenum with obstruction at third portion	Yes	0	Recovered
5 28 F	Malnourished; 60 lb. wt. loss	Malaria	Nausea, vomiting, abdominal pain and postprandial fullness intermittently 18 months	Duodenal obstruction third portion. Opacification of gallbladder 3 days after dye ingestion	Yes	Mesenteric lymphad-enopathy	Recovered
6 28 M	35 lb. wt. loss. Thin	Diabetes mellitus	Anorexia 8 months, abdominal pain 2 months, nausea and vomiting 6 days. Gastric analysis—normal free and total acid	Gastric and duodenal dilatation with retention at 6 hrs. Obstruction third portion duodenum. Prolonged retention gallbladder dye in stomach	Yes	0	Recovered
7 39 M	35 lb. wt. loss	Schizophrenia	Nausea and vomiting intermittently 6 yrs. Postprandial fullness 3 months. Gastric analysis normal	Obstruction third portion duodenum. Gastric retention 2 hrs. Reverse duodenal peristalsis	Yes	0	Recovered
8 58 M	Chronically ill	Tabes dorsalis, pyelonephritis	Abdominal pain, vomiting 5 days. Intermittent vomiting 10 yrs. Gastric analysis—no free acid, low total acid	Gastric and duodenal dilatation and retention of barium 6 hours	Yes	Mesenteric lymphad-enopathy	Recovered. Expired 1 year postoperatively of progressive renal disease
9 63 F	50 lb. wt. loss, 8 mos.	Atherosclerosis	Abdominal pain, 1 yr. Postprandial fullness	Normal roentgenograms	Yes	0	Improved
10 75 F	Thin	Arteriosclerotic heart disease	Abdominal pain, nausea and vomiting 1 week	None	Yes	0	Recovered
11 78 F	Emaciated	Carcinomatosis from uterine cervix	Abdominal distention 6 months. Vomiting and postprandial fullness 3 weeks	Gastric and duodenal dilatation and retention at 2½ hrs.	Yes	Retroper-itoneal lymphad-enopathy	Expired 11th postoperative day of carcinomatosis and ureteral obstruction

food. Occasionally the stools may be acholic, though this finding was not present in any of these patients. Some obtain relief by lying prone or assuming the knee-chest position. When examination is carried out in patients whose stomachs have not been decompressed by emesis or nasogastric suction, gastric distention may be evident. Otherwise nothing specific is noted. The diagnosis can often be suspected from plain roentgenograms of

TABLE III.—AGE DISTRIBUTION IN PATIENTS TREATED OPERATIVELY FOR THE SUPERIOR MESENTERIC ARTERY SYNDROME

Age, yrs.	*Acute*	*Chronic*	*Total*
0–10	1	—	1
11–20	3	3	6
21–30	1	3	4
31–40	—	1	1
41–50	—	—	—
51–60	—	1	1
61+	2	3	5
Total	7	11	18

the abdomen which may show gaseous distention of the stomach and duodenum with little or no gas beyond the point of obstruction. Roentgenograms are of less help when the stomach is distended with fluid alone or when the stomach and duodenum have been emptied by aspiration or vomiting. The diagnosis can almost always be established by roentgenologic study with contrast medium. The stomach and duodenum are large, the pylorus patulous. The obstruction is seen as a more or less straight line shutoff of the duodenum along the lateral border of the right psoas shadow. Fluoroscopically reverse peristalsis and churning of duodenal contents may be noted. Sometimes the contrast material will pass beyond the area of obstruction, especially if the patient assumes the left lateral or prone position.

Cholecystography may indirectly lead one to suspect some type of duodenal obstruction if the dye opacifies the stomach and duodenum or if the gallbladder reopacifies over a period of days. In 2 of the patients in this series such findings were noted.

Peptic ulcer is said to be a frequent concomitant disease but was present in none of our patients. Gastric analyses have been reported by Bockus in his series of cases, but no correlation was noted between these observations and symptoms present. Acidity was not as high as that found in patients with duodenal ulcer. In the few cases of ours so studied, gastric analysis revealed either normal findings or lack of free and low total acid. Very likely these findings may be the result of the bile regurgitation into the stomach.

Medical management may be successful, especially in the acute cases. Nasogastric suction should be instituted and intravenous fluids given to maintain water and electrolyte balance or to correct any imbalance present. In 2 of the acute cases, marked disturbance of the electrolyte and water balance was present at the time the diagnosis was made; such changes were not present in the chronic cases. If the patient has been bedridden he should be ambulated if this is feasible. If not, placing him in the left lateral or prone position may be helpful. After a period of thorough gastroduodenal decompression, oral intake may be tried provided the volume of aspirate suggests that the obstruction has been relieved. During the period covered by our survey a number of patients have responded to such medical treatment well, and operation has not been required. Such a response is illustrated by 2 recent experiences. One 22 year old male, who sustained multiple fractures of the pelvis and lower extremities necessitating immobilization in traction and cast, lay in the supine position for 2 months. At the onset of symptoms the diagnosis was quickly established, and nasogastric suction and intravenous fluid therapy were instituted. He was placed in the left lateral position, the obstruction was promptly relieved, and frequent small, high caloric oral feedings were started. After each meal he was placed in the left lateral position. His recovery was entirely uneventful. A poorly nourished 32 year old female patient had required operative resection of various portions of the small intestine for regional enteritis on several occasions. During convalescence from the last operation the classic superior mesenteric artery syndrome developed. After initial treatment with nasogastric suction and intravenous fluids, the obstruction was relieved and she was able to eat without difficulty provided she assumed the knee-chest position after each meal. On 1 occasion when this was impossible because she was receiving a blood transfusion, symptoms promptly reappeared and then disappeared

as soon as the regimen was reinstituted. As her convalescence continued and she was able to become ambulatory, she was able to eat without difficulty. Initial success with medical management does not invariably bring about permanent cure, however. One of the patients who was treated by operation had responded well to medical management and had had complete relief of symptoms for a period of 5 weeks only to have them recur.

When medical management fails, surgical intervention is indicated. Numerous methods have been proposed. In 1907, Bloodgood reported several cases treated surgically. In one a Finney pyloroplasty was performed with rather disastrous results. Such a procedure is unnecessary because the pylorus is patulous in these cases and ineffectual because the obstruction is distal. In surveying the literature of the 1920's concerning so-called visceroptosis, one is impressed with the likelihood that some of the patients treated by visceropexy did, in fact, have superior mesenteric artery obstruction, but not nearly as many as were reported as having this condition. In 1929, Delbert advocated multiple anastomoses which he termed gastropyloroduodenoenterostomy. Gastroenterostomy has been carried out with and without gastrectomy. Even though in the relatively recent literature there are several reports of relief of symptoms by this procedure, it would certainly not appear to be the treatment of choice since drainage can only be accomplished by retrograde reflux of duodenal contents into the stomach. One of our patients (Case 8, Table II) had been treated elsewhere by a gastrojejunostomy without relief of symptoms. The gastrojejunostomy was closed, a duodenojejunostomy performed, and the patient had complete relief of symptoms. It is our conviction that duodenojejunostomy is the best treatment not only for the superior mesenteric artery syndrome but also for other types of benign duodenal obstruction, such as duodenal atresia, duodenal stenosis, and annular pancreas. This anastomosis can easily be performed under local anesthesia which may be advantageous in a critically ill patient.

Duodenojejunostomy was first suggested as the best method of treatment for the superior mesenteric artery syndrome by Barker in 1906 and a year later by Bloodgood. It was apparently first performed in 1907 by Stavely. This procedure has subsequently been the most universally used surgical technique and has met with the greatest success and a minimum of complications.

The causative factors for the production of this syndrome are evident from certain anatomic considerations. The third portion of the duodenum is the most fixed part of the gastrointestinal tract, being attached to the dorsal wall of the abdominal cavity by peritoneum and having no true mesentery. The distal portion is fixed by the ligament of Treitz. It overrides the third lumbar vertebra and abdominal aorta which is directly dorsal to it. The junction of the second and third portions is fixed ventrally by the mesentery of the small intestine carrying the nutrient vessels and nerves. During embryonic rotation of the colon the mesentery and vessels of the midgut are positioned snugly against the duodenum. It is the angle formed by the mesentery and the included mesenteric vessels, on the one hand, and the aorta, on the other, which determines whether or not obstruction occurs at this point. The more acute the angle the more likely obstruction is to occur.

Codman in 1908 was the first to stress the change from the quadriped to the biped posture in man as an aggravating factor. The erect position leads to a more acute angle by traction downward and dorsally on the mesentery and its contents. Any abdominal constriction such as a corset might conceivably aggravate the situation. In a like manner, any position which increases the lumbar lordosis such as intrinsic vertebral column disease will decrease the arteriomesenteric angle. More recently, this

syndrome has been reported by Kauffman and Gerbode to occur secondarily to application of a body spica and the increased lumbar lordosis produced by hyperextension.

Any chronic disease which necessitates prolonged bed rest in the supine position contributes to the likelihood of development of duodenal obstruction. It is not infrequently noted in patients being treated for poliomyelitis and in mentally diseased or deficient patients who lie in the supine position for a prolonged period. The absence of mesenteric fat is said to increase the acuteness of the arteriomesenteric angle. Similarly, the presence of any mass in this area makes obstruction more likely, for example, abdominal lymphadenopathy and mesenteric hematoma.

It has been recently suggested that division of the ligament of Treitz and freeing the distal portion of the duodenum may bring about relief of symptoms. This is a proposal which deserves further trial. If obstruction cannot be adequately relieved in this fashion, it should be bypassed by duodenojejunostomy.

SUMMARY

The physiopathology, clinical symptoms, and characteristic features of the superior mesenteric artery syndrome have been reviewed. Some patients, particularly those having the acute type of obstruction, respond to a medical regimen. In cases in which nonoperative management is not effective, operative intervention is indicated. Experiences with the treatment of patients by duodenojejunostomy have been presented. In general the results were excellent.

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COMPLICATIONS OF BILIARY TRACT SURGERY

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As the morbidity of complications and the mortality rate are decreased after operations, surgical therapy not only becomes safer but it becomes easier from the patient's viewpoint. Operations upon the biliary tract are among those most frequently performed throughout the United States. Complications may be divided into two main groups. In the first may be placed those that are most common and may be anticipated and in the second those that are less frequent and not as predictable. In the former group are placed complications that are associated with inadequate preoperative preparation, the technique of operation, or some systemic condition unrelated to the disease of the biliary tract. The latter and smaller category includes those that are difficult to anticipate in any given patient but are nevertheless recognized as possible because they have been known to occur in any sizable series upon which meticulous records have been kept.

Many of those complications that may be anticipated can be prevented. Precision and accuracy in diagnosis and preoperative preparation, attention to detail, and meticulousness in surgical technique in performance of the operation, and close observation with well defined steps in management in the early postoperative period offer an opportunity to reduce them materially. To accept an incidence of complications and a rate of mortality that are but an average for reported series is to be satisfied with a *status quo* and to disregard progress.

A large proportion of the complications that follow biliary tract surgery are associated with alterations in normal function of the structures or parts involved as the result of either disease or the surgery performed.

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The interruption of the normal flow of blood or bile in their regular channels so that they are diverted into the operative area accounts for the most frequent complication, subhepatic accumulation. In addition, hemorrhage may occur because of a vitamin K deficiency, bile may escape to the exterior through a fistula, or jaundice may develop from an obstruction in the common duct. Thus the complications are as numerous and varied as the factors that cause them. Drainage tubes, for example, that are used to maintain decompression of the common duct may become dislocated, obstructed, or so difficult to remove that they are a cause of complications. Beyond the area of the surgical procedure lurk causes of complications that are to be kept in mind, such as varicosities that may be the origin of emboli or a narrowed coronary vessel that the burden of an operation may cause to occlude. The possible complications and the mortality rate following biliary tract surgery have been steadily reduced as this type of therapy has been extended.

SUBHEPATIC ACCUMULATION

A subhepatic periductal accumulation of material is the most frequent complication following operations upon the biliary tract (Fig. 1). This material consists of blood, bile, lymph, and peritoneal fluid. The hemorrhage stems from the blood vessels that have been injured or divided in the course of the operation. The liver, and specifically that portion to which the gallbladder is adherent, is frequently lacerated and injured. Bile is derived from the extrahepatic ductal system or the liver. The small bile ducts that enter the gallbladder directly from the liver and those that are prominent near the gallbladder site may be inadvertently opened during cholecystectomy. Lymph channels are rarely

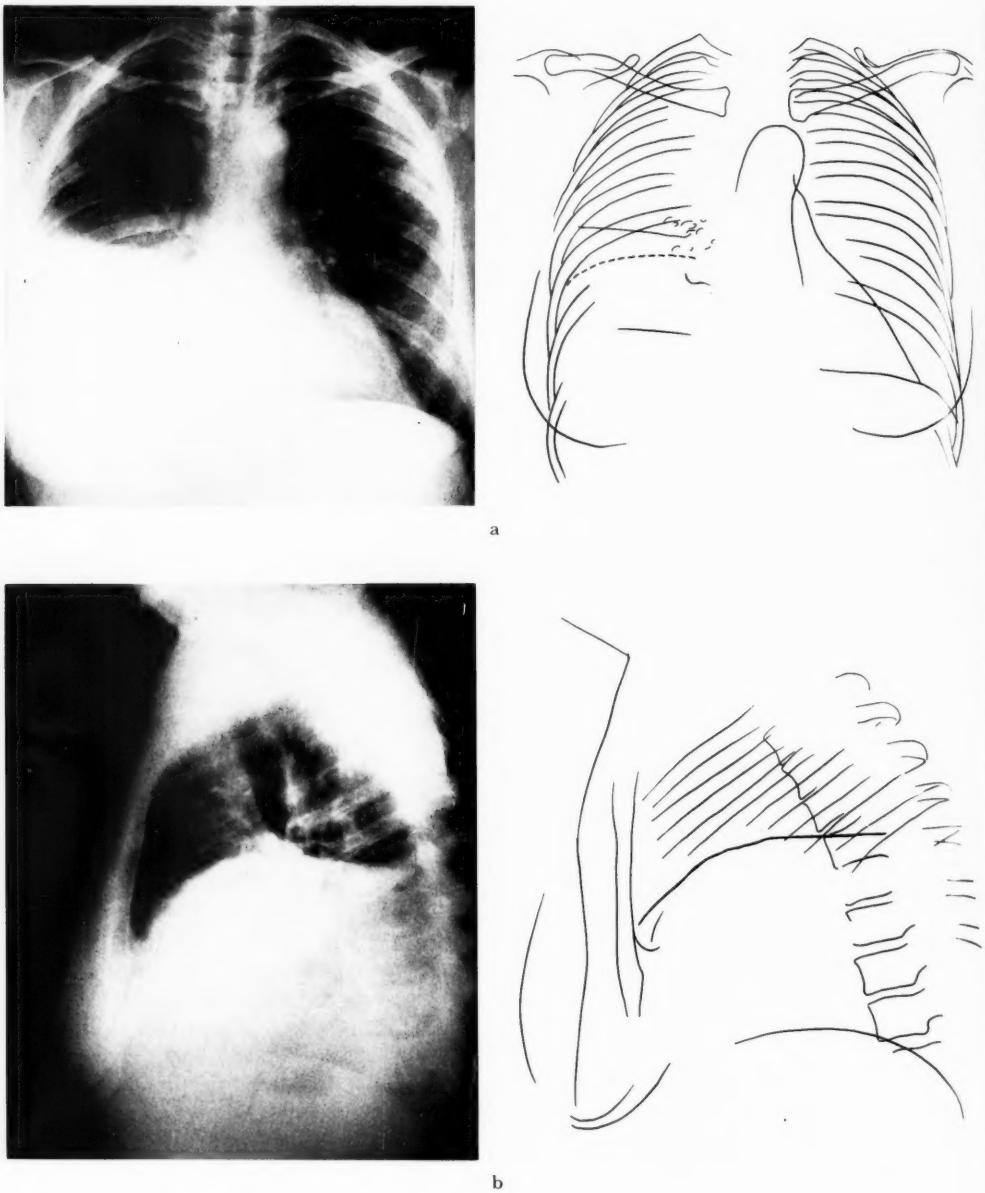

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FIG. 1. M. L., female, aged 50 years. Sixteen days after cholecystectomy performed in another hospital for cholecystitis and cholelithiasis, this patient was admitted to The New York Hospital because of abdominal pain, nausea, vomiting, jaundice, and dark urine. She was reoperated upon and a large subhepatic accumulation of 5,000 cubic centimeters of bile-containing material was evacuated. This was due to an injury to the common bile duct. After repair of the injury the patient recovered. a, Roentgenogram (anteroposterior view) and line drawing of subhepatic accumulation with marked elevation of the diaphragm. b, Lateral view.

FIG. 1. c, Roentgenogram and line drawing showing displacement of the stomach to the left by subhepatic accumulation.

grossly visible at operation, but they are luxuriant in the area about the gallbladder. The irritative reaction to blood, lymph, and bile may cause an increase in the permeability of the peritoneum, resulting in an escape of plasma. If bacteria are present in addition, this response may be more marked. The effects of all of these factors in contributing to the accumulation will vary with their degree. If only small amounts of blood, bile, and lymph are present and there is little or no bacterial growth, the peritoneum will absorb and remove them efficiently. If, on the other hand, one or all are present in large quantities and evoke an outpouring of plasma rather than an absorption of these substances, then the amount of accumulation increases.

It is a common practice to place a drain of some kind in the subhepatic area and to have it extend through the abdominal wall to facilitate the evacuation of such accumulations. For many reasons these drains not infrequently fail to fulfill their intended function. They may not be properly placed or they may be dislocated. Sometimes they evoke an increased foreign body reaction on the part of the peritoneum, thus leading to a further sealing off of a localized accumulation. In still other instances, the drain may be removed before the accumulation develops to any significant size. In any event, a subhepatic accumulation frequently takes place. If it persists or increases to an important degree, there is discomfort and pain in the right upper quadrant, an elevation of temperature, and a leucocytosis. There is then a localized peritonitis. At any stage in its process the accumulation may regress or establish escape of its contents externally, or extend to involve the subdiaphragmatic area or even spread into the abdominal cavity. A severe reaction of the tissues near the origin of this accumulation may result in obstruction of the common duct or reflex spasm of the sphincter of Oddi. If the bacte-

rial content of the bile is high and there is also a cholangitis, then the systemic manifestations may be marked.

Some degree of subhepatic accumulation occurs in the majority of patients subjected to operations upon the biliary tract. It is a matter of extent that determines whether or not it becomes clinically significant. In my opinion it reaches these proportions in 7 to 10 per cent or more of patients operated upon. It has been the most frequent complication to be diagnosed in the experience at The New York Hospital, and the most frequent cause leading to requests for my consultation elsewhere following biliary tract surgery.

Its prevention is dependent upon careful surgical technique and the maintenance of drainage of the subhepatic area for 3 to 4 days or more after operation. When an accumulation is sufficiently extensive to make diagnosis certain, surgical drainage should be seriously considered.

HEMORRHAGE

It is an old adage that hemorrhage is one of the important hazards of surgery. Operations upon the biliary tract are no exception to this statement. An analysis of the complications following surgical therapy for biliary tract disease as reported in any sizable clinical series reveals that hemorrhage continues to contribute materially to the morbidity rate. The recognition of hemorrhage after operations upon the biliary tract depends upon the same systemic manifestations that are associated with hemorrhage from any other area. There is an increase in pulse rate and a fall in blood pressure. The patient is often apprehensive and thirsty and may exhibit air hunger. The relief of these manifestations by blood replacement should be a confirmation of the diagnosis whether hemorrhage has been continuous since operation or began later. Bleeding in the immediate postoperative period may result from other sources such as a duodenal ulcer or diverticulitis, but this is rare.

The more common sources of hemorrhage associated with biliary tract surgery include the cystic artery, anomalous branches of the hepatic and right hepatic arteries, the gallbladder bed, the liver, and the vessels of the common duct and of the abdominal wall. An occasional hemorrhage has been reported from injury to the inferior vena cava. Hemorrhage sufficient to require blood replacement is an indication for immediate reoperation and search for the source of blood loss. There are two reasons for this approach. First, the hemorrhage may continue or recur and exsanguination may result in death. Second, blood in such amounts is not readily absorbed by the peritoneum, and if it is mixed with bile that contains organisms a subhepatic or subphrenic abscess may follow.

This complication may be prevented by carefully identifying all blood vessels before division, and then securing them by ligature or transfixing suture. There are so many variations in the blood vessels in the subhepatic area and in their relation to the biliary tract that it is hazardous to divide any structure that is not identified. Furthermore, divided structures should be meticulously occluded to prevent escape of the fluid they may contain, be it blood, bile, or lymph.

Although the more frequent sources of hemorrhage are the cystic artery, anomalous branches of the hepatic artery, vessels within the wall of the common bile duct, and aberrant vessels that reach the gallbladder through the bed of the liver, it may also result from injury to the liver by incision or laceration as the surgeon removes the gallbladder. Such bleeding may be noted at operation, and though it usually subsides rather quickly, it may begin again within a matter of hours when bile causes the clot to separate from the liver surface.

Hemorrhage due to vitamin K deficiency. Patients with jaundice usually have an increased tendency to hemorrhage. If the degree of icterus is great and of long-standing, this may be marked. The clotting and bleeding times of these individuals are usually normal, but the clot retracts poorly and is fragile. Such clots do not seal the open end

of the divided vessels and there is oozing. Fluctuations of the blood pressure may result in complete dislodgment of the partially occluding clots, and any vessel not carefully ligated may bleed actively.

The parenteral administration of vitamin K to jaundiced patients assures control of the tendency to increased bleeding caused by reduced prothrombin, as long as their liver function remains good. Since it was generally accepted in 1936 vitamin K therapy has been so effectual in patients with jaundice with a hemorrhagic tendency that the fatalities attributable to this have almost completely disappeared.

All patients being considered for operation upon the biliary tract should have careful measurements of their prothrombin, and if it is lowered vitamin K should be given. If the administration of vitamin K does not result in a satisfactory elevation of the prothrombin, operation should be postponed. At present we recommend that patients with a prothrombin level of 20 per cent below normal be given vitamin K parenterally. There should be a rapid response, and if this does not occur, the extent of liver damage is probably so extensive that surgery will not be well tolerated.

BILE PERITONITIS

The escape of bile into the peritoneal cavity from the common duct, the cystic duct remnant, small radicles extending directly from the liver to the gallbladder, and breaks in the continuity of liver substance results in a peritonitis. If the rate of escape is slow, there is a strong likelihood that the reaction to bile of the omentum and the peritoneal surface of the viscera adjacent to the area of operation will prevent its escape into the remainder of the abdomen. Thus a localized accumulation of bile may occur. The greater the area of peritoneal surface that comes into contact with bile the greater is the effect likely to be. The local accumulation of the bile by walling off of an area by the omentum and adjacent viscera is a response of the body to keep this hazard at a minimum. Free bile in large amounts within the peritoneal cavity may cause a fall in blood pressure and the clinical manifestations of shock, and may terminate in death. While this is the result most to be feared, large quantities of bile may also escape into the peritoneal cavity causing marked abdominal distention but little evidence of peritoneal irritation and no changes in blood pressure. Clinicians have been perplexed by the fact that these two situations may occur from comparable amounts of bile liberated into the peritoneal cavity. Much study and research have been directed at the solution of this problem. No one explanation seems to account for the various effects that free bile in the peritoneal cavity can produce. In some instances, as bile escapes into the abdomen, the patient appears to become more and more restless and uncomfortable. Pain, generalized over the abdomen, is frequent. The temperature becomes elevated. The pulse may become rapid or slow, but the blood pressure falls. It is believed that this picture of shock results because bile increases the permeability of the peritoneum, thus permitting the rapid escape of plasma with a reduction of the circulating volume. When this continues, death from shock may result. The time lapse between the beginning of liberation of bile into the abdomen and the appearance of shock varies greatly; in some it is a matter of hours, and in others it may extend over a period of from 7 to 10 days. It is generally agreed that infection, or even the presence of bacteria, may accelerate this course of events. On the other hand there are instances in which accumulations within the abdomen of bile in amounts up to 6,000 to 8,000 cubic centimeters appear to be innocuous and produce only those symptoms that are attributed to abdominal distention by fluid. Analysis of bile removed from the abdominal cavity has not revealed any consistent difference between that removed from the moribund patient and that removed from one with few symptoms. Bile salts, bile acid content, and the bacteria present have been studied with considerable care. Why some patients toler-

ate bile within the abdomen and others do not has yet to be clarified.

Treatment of bile peritonitis is dependent upon the reaction that results. Shock is best treated by replacement of reduced circulating volume. At operation, it is essential to remove the bile that has accumulated in the abdomen and to divert its flow to the exterior if it cannot be channeled into the intestinal tract.

BILIARY FISTULA

When bile escapes from its normal course, it either accumulates near its source, spreads over the peritoneum, or reaches the exterior, usually by means of a drain. If the local accumulation persists and increases, then it may form a tract to the exterior. When bile is free in the peritoneal cavity, operation may reveal its source and correct the condition by redirecting its flow into the intestine or diverting it to the exterior. In all 3 instances, however, a biliary fistula may result. This complication may be burdensome to manage and difficult to correct, but it reduces the seriousness of the situation by replacing a condition associated with a high mortality rate by another with a much lower mortality rate.

An external biliary fistula that develops after an operation upon the biliary tract is the result of an interruption of the flow of bile through its normal path from the liver to the duodenum. It may occur after any operation upon the biliary tract, and the cause may be the nature or extent of the biliary tract disease, or distortion or injury resulting from the surgical procedure.

Fistula after cholecystectomy means obstruction distal to the cystic duct, in most instances, usually by stone or scar. The diagnosis and exact location of the obstruction are established by: (1) injection of radiopaque material into sinus opening; (2) intravenous cholangiography; (3) gastrointestinal series. Direct treatment consists of removal or correction of the cause.

Biliary fistulas are frequent after cholecystostomy. In the majority of instances the abdominal wound which is the site of the tube draining the gallbladder closes a few days after the latter is removed. Within days or weeks the site reopens and bile and mucus are discharged. In 50 per cent of patients, gallstones re-form within 2 years after the gallbladder has been evacuated of stones and drained by cholecystostomy. It is probable that stones in the gallbladder act as ball-valves and obstruct the return flow of bile into the common duct. Cholecystectomy should be done within a period of 6 months after a cholecystostomy to prevent this complication. Cholecystectomy is, of course, indicated when biliary fistulas follow cholecystostomy.

Cholecystectomy is by far the most frequently performed operation upon the biliary tract. Biliary fistulas that follow this procedure are usually the result of obstruction to the flow of bile distal to the cystic duct junction with the common duct. Calculi, neoplasm, and scarring within the distal segment may cause obstruction that results in a rupture of the occluded cystic duct remnant with the escape of bile through a fistula to the exterior. Actually the common causes of obstructive jaundice following cholecystectomy may result in a fistula if the integrity of the wall of the obstructed duct is lost. Thus an obstructive jaundice may precede the formation of a biliary fistula. The amount of bile that escapes from the fistula in the now jaundiced patient is an indication of the degree of obstruction or distortion of the normal path.

When the gallbladder or any significant amount of its mucosal lining is not removed, a fistula that discharges mucus or mucus and bile may develop. It is not unusual to operate upon patients who give a history of having had a cholecystectomy for cholecystitis and cholelithiasis and to find a fistulous tract leading from the abdominal wall to a remnant of the gallbladder, usually the ampullary portion, which contains calcareous material. Such patients become symptom-free after removal of the remnant of the gallbladder and its cystic duct down

to within 3 millimeters of its true junction with the common duct.

Carcinoma of the common duct may be the cause of a biliary fistula following the removal of a gallbladder and exploration of the common duct for a mild or intermittent jaundice and symptoms compatible with biliary tract disease. Calculi may or may not be present in the gallbladder. Exploration of the common duct does not reveal an evident cause but the obstruction is not then complete. However, as the carcinoma grows obstruction increases.

The establishment of a biliary fistula soon after an operation upon the biliary tract is always a cause for grave concern. The greater the amount and proportion of bile that is lost through it, the more serious is its import. It is an indication that an opening has been produced in the ductal system and that there is probably obstruction distal to the defect. Jaundice preceding the discharge of bile usually indicates occlusion and possible interruption of the common duct. If there has been no preceding jaundice, the discharge of bile is more likely to be the result of an unligated cystic duct or a defect in the wall of the common duct due to operative injury. Division of small bile ducts leading from the liver to the ampulla of the gallbladder may give rise to the formation of a subhepatic accumulation of bile and then a fistula. The amount of bile usually decreases gradually over a matter of 10 to 20 days and the fistula closes. Injury to the intrahepatic ducts either in the area of the gallbladder bed by too deep dissection, or elsewhere within the operative field by improper retraction may also lead to the formation of bile fistulas. These, too, are usually of short duration and require no surgical interference other than the maintenance of free drainage until the escape of the bile ceases.

After the transduodenal approach for operative procedures upon the ampulla of Vater and the sphincter of Oddi, including the removal of calculi from that part of the common duct that is within the duodenal wall, dehiscence of the duodenostomy wound may occur. A fistula may thus be established that is, strictly speaking, duodenal in origin, but discharges bile as well as other intestinal juices. Fortunately, this complication is less frequent than it was formerly because of the more meticulous closure of the incision in the duodenal wall.

A duodenal fistula is to be suspected when bile and intestinal drainage appear after an operative procedure upon this segment. The diagnosis is readily confirmed by roentgenologic examination, using radiopaque material to visualize the course of the tract and its opening from the duodenum. Although these may close without operation, they are usually quite slow in doing so. The loss of fluids and electrolytes may so deplete the patient that surgical correction rapidly becomes mandatory.

Nutritional depletion rapidly follows the complete diversion of the bile from the intestinal tract. As it escapes from a fistula, bile should therefore be collected and returned to the patient at regular intervals. Many methods have been evolved for this objective, ranging from having the patient drink the bile to introducing it into the stomach through a small tube. In our hands, the latter has been the more satisfactory. An external biliary fistula is an urgent clinical problem and requires surgical correction as early as it can be accomplished with safety to the patient. Thus, while the nature of the fistula is being studied, the patient should be prepared for operation. This may be difficult because massive infection may also be present, and it may require herculean efforts to attain a satisfactory nutritional, fluid, and electrolyte state.

In attempting to determine the cause of a biliary fistula, it is of first importance to know what the findings were at the primary operation and exactly what operative procedure was done. Sometimes this information is not available, and the surgeon must rely upon diagnostic measures for guidance. In the absence of jaundice, intravenous cholangiography may give much informa-

tion, revealing calculi, distortion of the ductal system, or abnormalities sometimes unexpected. Additional information may be gained from a gastrointestinal series focusing in particular upon the duodenum. Roentgenographic visualization of the fistulous tract with radiopaque material is usually the most informative method.

If the cause of the biliary fistula can be determined, then the surgeon's problem becomes evident and he may plan his attack. On the other hand, an attempt at correction of a biliary fistula without obtaining all possible information may result in a frustrating experience to the surgeon and prove of no benefit to the patient.

The surgical procedure for correction of a biliary fistula depends upon its cause. If it is due to a calculus, the stone should be removed; if the common duct has been injured, it should be repaired. Emphasis is placed upon such an approach because attempts are still being made in this country to dissect out fistulous tracts and implant them into the intestinal tract. Such attempts rarely meet with success because the tract tends to contract and become obliterated, thus producing obstructive jaundice.

DISLOCATION, OBSTRUCTION, AND RETENTION OF DRAINAGE TUBES

Dislocation of common duct tubes. Tubes placed to provide decompression and drainage of the common duct may be displaced, occluded, or become difficult to remove. It is the common practice to maintain decompression and afford drainage of the common duct after its exploration by means of a T tube placed through the incision in its wall or by a catheter placed through the cystic duct into the choledochus. The tube may be displaced by any one of a number of inadvertent occurrences. It may be caught in the bed clothing or it may be attached to some part of the bed so that as the patient turns, the tube is dislocated. Sometimes the patient may pull upon the tube. There are many methods by which the tube may be secured so that this will rarely occur. The tube may be anchored to the skin by sutures, or fastened to a roll of bandage held to the skin by adhesive. It is worthwhile to instruct the patient before operation concerning the function of such a tube.

The shorter the lapse of time from operation until the inadvertent displacement of the tube, the more serious is the accident likely to be. The formation of a tract along the course of such drains tends to allow the bile that escapes from the common duct to pass to the exterior rather than to accumulate in the periductal and subhepatic area.

When any tube draining the common duct is inadvertently displaced and there is no obstruction distally, one may expect that little bile will escape. On the other hand, if there is obstruction in the distal part of the common duct, then the amount will be large. The size of the defect in the wall of the choledochus is of less importance than the degree of obstruction. Thus bile loss depends on the patency of the choledochal duodenal junction and the presence of calculi in the distal common duct.

The question may arise as to whether tubes that have been displaced from the duct and remain within the abdomen should be left alone or removed. Because bile may be expected to drain into the subhepatic area, the tube may serve a useful purpose in facilitating the escape of bile through the abdominal wall. A further protection is provided by drains that extend from opposite the foramen of Winslow along the bed of the gallbladder through the abdominal wall.

Patients who have this unfortunate accident should be observed carefully. If there is no external drainage of bile and there is evidence of diaphragmatic irritation, abdominal distention, or any other sign of the escape of bile into the peritoneal cavity, operation should not be postponed. In many patients bile will drain to the exterior for a few hours, and thereafter recovery will be satisfactory. In others bile peritonitis may develop that is of a general nature or

is localized to the subhepatic and subdiaphragmatic area.

Obstruction due to occluded tubes. In the early postoperative period, tubes may become occluded by blood clot, calcareous gravel, or distortion. The introduction of sterile saline under gentle pressure will usually suffice to correct this. The longer a tube remains within the ductal system, the more likely it is to become obstructed by encrusted material. However, tubes have been found to remain patent for years. Those that become clogged by encrusted material should be removed because additional layers of encrustations may result in complete occlusion of the common duct. The use of solvent materials other than water and saline is not recommended.

Retention of drainage tubes. Some surgeons seek security from the inadvertent displacement of tubes in the bile duct by suturing them in place. When plain No. 000 catgut is employed, the tube usually is readily removed after 10 days. If they cannot be withdrawn readily, it is better to let a few days elapse and then make another attempt. Force should not be applied.

A bile-tight closure about a T tube is advocated in order that periductal accumulations be kept at a minimum. Since large or stiff T tubes may be difficult to withdraw, the surgeon should select tubes that are flexible and of suitable size. It is a good practice to cut a small V-shaped segment in the T tube wall opposite the limb that will lead to the exterior. Half of the circumference of the tube within the duct may be cut away before it is placed in order to facilitate later removal. When removal is not readily accomplished, slight traction upon the external limb of the tubing followed by setting a clamp across it and having the patient walk about may initiate its dislocation.

JAUNDICE FOLLOWING OPERATIONS UPON THE BILIARY TRACT

The appearance of jaundice following an operation upon the biliary tract is usually an indication of a serious complication. The nature of its onset, its intensity, and severity or degree of systemic manifestations that may accompany it provide a basis for suspecting its cause and probable course. The causes are numerous and include obstruction of the extrahepatic ductal system, cholangitis, intrahepatic cholangiolitic hepatitis, hepatic failure, intrahepatic metastatic carcinoma, viral hepatitis, toxic hepatitis due to medications, blood dyscrasias, transfusion reaction from improperly matched blood, pyelophlebitis, and other more rarely encountered conditions.

The most frequent cause of jaundice following cholecystectomy or operations upon the biliary tract is obstruction some place along the extrahepatic ductal system. Calculi, infection, neoplasia, and scarring may cause such obstruction, not only within the system but at its outlet into the duodenum at the ampulla of Vater. Lesions extrinsic to the hepatic ducts such as expanding lesions of the pancreas, carcinoma, or pancreatitis may encroach upon the lumen and produce an obstructive jaundice. Occasionally a neoplasm of the duodenum may occlude the biliary outlet. During cholecystectomy, injury of the common duct that results in its narrowing or complete interruption occurs often enough so that it should always be considered as a possible cause whenever jaundice appears within a day or two after operation.

Calculi. The single outstanding cause of jaundice following cholecystectomy alone or in combination with common duct exploration is calculi within the ductal system. Although many patients may have had jaundice before operation, perhaps an equal number may have had no symptoms of common duct stones. Careful evaluation of the findings at operation, seeking specific evidence of common duct calculi, should reduce this complication. When symptoms have been overlooked, it may be expected that these will increase as well as recur. It is difficult to explain why calculi, that have been "silent" although present within

the ductal system, should sometimes obstruct the bile flow following cholecystectomy. It has been suggested that cholecystectomy causes increased spasm of the sphincter of Oddi, which in turn results in an increase of pressure within the ductal system with the dislocation of the stone to a position that obstructs the flow of bile. Manipulation of the duct during operation and the use of instruments within the duct may also cause edema and swelling that may reduce the lumen so that calculi that were free and moved readily before now become impinged or impacted in the lower segment. If stones remain in the common duct, it may be expected that most of them will in time cause symptoms and some will result in complete obstruction. Because the incidence of common duct calculi increases with age, there is some justification in following a policy of exploring the common duct on the slightest evidence of their presence in the older age group. When operation includes common duct exploration, the overlooking of stones can be reduced by meticulousness and thoroughness in searching for them, employing operative cholangiography or any adjunct measures that the surgeon has found of value in his hands (Fig. 2). By such means, the incidence of jaundice due to overlooked calculi may be kept low but probably will not be entirely eliminated. Examination of the ductal system by cholangiography before the removal of the catheter or T tube used to drain the common duct will reveal most of these. Information concerning the presence or absence of calculi is of value if jaundice appears later.

If calculi are demonstrated within the common duct after an operation upon the biliary tract and before the patient is discharged from the hospital, they should be removed unless there is some contraindication. Some patients will prefer to postpone a second procedure. If a tube draining the common duct is in place, this should not be removed until the secondary operation is embarked upon. It is recognized that calculi may exist in the common duct without causing symptoms, but this is unpredictable. Jaundice, constant or intermittent, renders operation imperative.

Postoperative cholangiograms should be done before the removal of any drainage tube from the common bile duct. These examinations require care in their performance which is the responsibility of the surgeon. If the radiopaque material is introduced by means of a syringe under pressure greater than that of 30 centimeters of water, the ductal system may be distended. If organisms are present or if there is a cholangitis, the patient, after experiencing pain, may have a chill and the temperature may rise to 40 degrees C. or more. While the same mechanism might well result in pancreatitis, it has not been observed. Usually the flare-up of cholangitis that follows overdistention of a ductal system that has been well decompressed for several days is of short duration and requires no special therapy.

Patients in whom symptoms and signs of common duct stone develop after cholecystostomy without choledochotomy. A patient who has had a cholecystostomy may discharge bile in varying amounts immediately after operation and for a few days thereafter. If this becomes a complete diversion leading to a loss of 800 to 1,500 cubic centimeters, then it is quite likely that the common duct distal to the cystic duct is occluded. Here, again, the more frequent cause is calculi or calcareous material, although neoplasm or inflammatory reaction may be culpable. Roentgenographic examination using some radiopaque substance will usually establish the diagnosis. In suspected neoplasm, visualizing the lower part of the stomach and duodenum by a gastrointestinal series combined with cholangiography may demonstrate its nature more clearly. The gallbladder and the ductal system should be visualized before a patient who has had a cholecystostomy is discharged from the hospital. The tube draining the gallbladder should be removed only after it has been established that there

are no stones or evidence of obstruction within the biliary tract. It is perhaps a better practice to leave the tube in place until cholecystectomy is performed.

A careful record should be kept of the amount of bile discharged through a cholecystostomy. A gradual decrease in bile output accompanied by an increase of bile in the stools is indicative of restoration of normal bile flow. Intermittent flow of bile with periods of complete obstruction is typical of a calculus in the lower segment of the common duct. Gradual and increasing bile loss is usually caused by calcareous, sandlike material or neoplasm.

Patients in whom signs and symptoms of common duct stone develop after cholecystectomy without common duct exploration. Following cholecystectomy, pain in the right upper quadrant that is sudden in onset and that increases in severity and radiates through to the back and the angle of the right scapula is very suggestive of choledocholithiasis. If there is an elevation of temperature and jaundice that persist even for ever so short a time, then one may conclude that the diagnosis has been established. If the jaundice subsides shortly, an intravenous cholangiogram is most dependable to confirm the diagnosis. This often demonstrates the location, size, and number of calculi. If the stone is located in the ampulla of Vater, there is often associated spasm of the sphincter of Oddi with common duct dilatation (diameter of 1.2 cm. or more). The precipitation of attacks of pain by eating is quite characteristic of small stones within the ampulla of Vater.

The measurement of the diameter of the common duct as visualized by intravenous cholangiography may lack accuracy because of a number of factors. However, 8 millimeters is probably the upper limit of normal. Patients who have had the gallbladder removed have been observed to have diameters up to 12 millimeters without evident explanation. Measurements greater than these values for the two respective situations are evidence of obstruction.

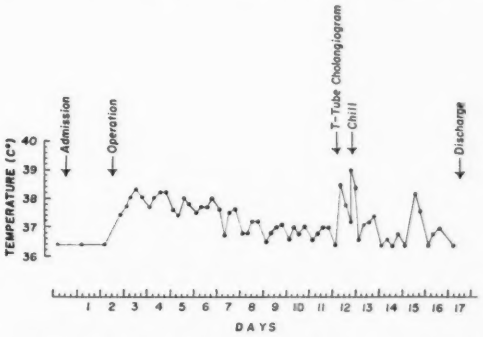

FIG. 2. Elevation of temperature after postoperative cholangiogram. Ten days after operation, 30 cubic centimeters of radiopaque material were introduced by means of a syringe through the T tube. The patient immediately experienced slight pain. The cholangiogram showed a normal ductal system with a patent duodenojejunal junction. Within 2 hours the patient had a severe chill followed by a temperature elevation to 38.8 degrees C. There was a complaint of slight discomfort in the hepatic region for a period of 24 hours. There was a slight chill 12 hours later with elevation of temperature to 39 degrees C. Thereafter the patient's course was uneventful.

When jaundice is present, even if the obstruction is not complete, intravenous cholangiography is of no value because the opaque material is not excreted in sufficient amounts to visualize the ductal system. Absence of bile in the stool and an increasing jaundice, even with the subsidence of fever and disappearance of pain, are an indication for surgical intervention.

Patients in whom jaundice develops after choledochotomy without cholecystectomy or cholecystostomy. Secondary operations on the biliary tract undertaken for obstructive jaundice although generally effective are followed by a higher incidence of complications than primary surgical procedures. There are several factors that account for this. First, biliary tract disease has been present for a longer period of time, with its associated changes. Second, the tendency to form new stones seems to persist more frequently in this group. Third, intrahepatic dilated segments of the ductal system that favor calculi formation may be present.

Neoplasm of the ampulla of Vater. Jaundice that follows cholecystectomy performed for

acalculous cholecystitis should alert one to the probable presence of a malignant neoplasm of the extrahepatic ductal system or the ampulla of Vater. Sometimes, however, at operation, a gallbladder associated with neoplasm causing obstruction may not only be somewhat enlarged but may contain stones. The common duct is usually full or distended, but its walls are not unusual. After cholecystectomy, mild and intermittent jaundice appears. It increases over a matter of weeks. Re-evaluation consistently reveals occult blood in the stools and increased discomfort in the right upper quadrant after eating. Gastrointestinal series may or may not demonstrate a lesion in the ampulla of Vater. At a second operation, the common duct is further enlarged and a tumor is readily palpable in the region of the choledochal duodenal junction. Transduodenal exposure of the ampulla of Vater provides an opportunity to confirm the diagnosis immediately by biopsy and frozen section. Carcinoma of the ampulla of Vater should be treated by the Whipple procedure. This provides for wide excision with restoration of continuity of the gastrointestinal tract and conservation of the external secretion of the remaining pancreas.

PANCREATITIS

Pancreatitis fortunately is not a common complication following cholecystectomy. It does occur, however, although with somewhat less frequency than after exploration of the common duct. Regurgitation of bile is believed to be the most frequent cause. Because of its tendency to subside within a few days after onset and because the jaundice is almost never marked, no surgical intervention is indicated. Occasionally, pancreatitis following biliary tract operations may be of a fulminating type and end fatally.

INJURY TO THE COMMON DUCT

In the course of performing a cholecystectomy, the cystic duct should be so dissected that its junctions with the common duct and the ampulla of the gallbladder are clearly demonstrated. To accomplish this, the cystic duct is isolated from any structures adjacent to it. In most instances, the cystic artery courses parallel to it for about half its length, and the sentinel lymph gland rests between these structures at Calot's triangle. If the cystic duct is not properly dissected, then the common or right hepatic bile duct may be mistaken for it and divided. When the true junction of the cystic with the common duct is not demonstrated, the operator in placing a clamp across it may distort it just enough to result in the wall of the common duct being included. A ligature placed proximal to the clamp further distorts the duct and diminishes the lumen. Gross distortion of the common duct by traction upon the cystic duct can result in excision of the segment of the common duct. Blind clamping of bleeding vessels may readily injure the common duct, particularly when hemorrhage from the cystic artery or anomalous branches from it, or from the right hepatic artery obscures the field. Under such circumstances a ligature may inadvertently be placed so as to occlude both the vessel and a part or all the lumen of the common duct.

Stricture of the bile duct. One of the most serious complications associated with operations upon the biliary tract is stricture of the bile duct. Its genesis is tragic for both patient and surgeon. The events that precede the development of a stricture have been discussed under cholecystectomy. The prevention of this complication is the responsibility of anyone who operates upon the biliary tract. The clinical course that follows injury to the bile ducts that results in stricture formation is distressing and disabling. Perhaps less than half of those who sustain a stricture due to operative injury survive for 10 years. Biliary obstruction or infection that persists or recurs causes progressive liver damage.

Diagnosis. Injuries of the bile duct that are recognized and repaired at the time they occur have a definitely better prog-

nosis than those that are first demonstrated at a secondary operation. When injury is not recognized during the primary operation, one of two manifestations may appear shortly thereafter. The first and the most frequent is jaundice, and the second, which may or may not be preceded by jaundice, is a biliary fistula that diverts a large amount of bile. As to the first, there is occlusion of the bile duct by ligature or by excision of a segment and ligation of the choledochus which has been mistaken for the cystic duct. Distortion of the main bile ducts by angulation due to traction upon the cystic duct is relatively rare. Rather the more common course of events seems to be that the common duct, being mistaken for the cystic, is clamped and divided and then occluded by a ligature. Many injuries are recorded as following uncontrolled hemorrhage from the cystic or hepatic artery where the operator has placed a clamp blindly, perhaps making several attempts before the bleeding is checked. A ligature is sometimes placed without accurate identification of what structures have been included in the clamp. The common duct may thus be completely or partially occluded. When a ligature has been placed about the common duct, necrosis may occur and a bile fistula form. Under such circumstances, the following manifestations occur. Immediately or shortly after operation, the patient complains of pain that is deep-seated in the right upper portion of the abdomen. The pulse rate is elevated and the patient experiences increasing discomfort and restlessness that is not relieved by medications ordinarily employed immediately after operation. Within 12 to 24 hours, an evident icterus is present and there is bile in the urine. If necrosis of the wall of the bile duct takes place, then the obstructed bile flows into the subhepatic area. If drains are present, this in turn escapes externally and a bile fistula is established. If the bile does not accumulate in the subhepatic area but flows freely into the general peritoneal cavity, then a bile peritonitis results. When the common bile duct has been completely divided or occluded, a bile fistula must be established if the patient is to survive. Incomplete occlusion or removal of a part of the wall may be followed by a biliary fistula, and at the same time part of the bile may reach the duodenum. As scarring takes place, the bile lost externally and passing into the duodenum may decrease and stop altogether, and concomitantly jaundice may increase and become complete.

Management. In our experience over a period of 30 years in the treatment of patients who have had an injury to the bile duct at the time a cholecystectomy was done, I have not encountered at a secondary operation any two with exactly the same findings. Those patients who have been operated upon for jaundice a week or longer after the primary operation have, in some instances, been subjected only to exploration and the establishment of a free flow of bile to the exterior. Only occasionally have I embarked upon a definitive procedure to reconstruct the common duct. There have been several reasons for this, namely the general condition of the patient and the difficulty found in attempting to dissect the structures involved sufficiently to permit performing a satisfactory anastomosis.

Those patients who have an external bile fistula through which most of the bile escapes are much better able to tolerate the operation after preparation, and the repair is less arduous.

Regardless of the patient's appearance of well-being, all possible information should be obtained about the primary operation, the course of events that followed, and the patient's present status. Correction of a stricture of a bile duct is always a major undertaking, and the surgeon who attempts it should take all measures to provide every advantage to the patient and to himself. If no jaundice is present, the biliary tract should be visualized in so far as it is possible by intravenous cholangiography. Fistulous tracts should likewise be explored by opaque

material. The liver status is important and may determine how extensive an operation the patient may be expected to tolerate with safety. Indeed, a liver that has been obstructed for a long period and is also the site of cholangitis is a contraindication to any prolonged procedure.

Repair (Fig. 3). Usually one may readily demonstrate the proximal segment at the hilus of the liver, and indeed dense adhesions here are not frequently encountered in the first attempt at a repair. A fistulous tract, if present, leads one directly to the proximal segment. Once this is demonstrated, a reinspection to identify the portal vein, gastroduodenal artery, and hepatic artery will enable the surgeon to locate the right hepatic artery. It is extremely important to demonstrate this vessel before it or its branches enter the scar tissue. With these structures identified, dissection of the proximal segment and demonstration of the right and left hepatic ducts are more readily accomplished.

If the duct has been completely divided, the distal segment is often contracted toward the duodenum. Its identification may be difficult. Transduodenal exposure of the ampulla with retrograde catheterization of the common duct may be necessary. This may demonstrate that there are several centimeters between the ends of the divided duct when they are dissected free. The duodenum, which has already been mobilized, may be displaced toward the liver hilum to compensate for the exaggerated apparent defect. The ends of the common duct are dissected free of scar tissue, and an end-to-end anastomosis is accomplished with interrupted sutures of No. 5-0 arterial silk over a T tube which serves as a prosthesis and provides for decompression. The long arm of the T tube is brought out through a small incision proximal to the line of anastomosis if that segment is long enough to permit. Otherwise it is brought out in a similar manner below.

When the common duct has not been completely divided but is obliterated for some distance by scar tissue, resection of the scarred segment is indicated. The amount removed is dependent upon the involvement; the immediate objective is to have segments of as nearly normal choledochus as possible with which to establish an anastomosis. It is essential for the success of an anastomosis of the common duct that the suture line not be under tension or the duct subject to distention. These conditions are best established by adequate mobilization of the duodenum and the placing of the distal arm of the T tube through the choledochoduodenal junction.

OTHER CAUSES OF JAUNDICE

Transfusion—hemolysis and incompatible blood. Jaundice that results from a hemolytic reaction following transfusion becomes apparent within 12 to 24 hours. If it is mild and the total amount of hemolysis is not great, it will clear within from 2 to 5 days. There is a hemoglobinuria that precedes the appearance of the jaundice and is of short duration. If the hemolysis is the result of a severe reaction due to incompatible blood, then hemoglobinuria is followed by renal shutdown and anemia. The jaundice under these circumstances is greater but not marked. It usually persists, however, until renal function is re-established. If renal failure is complete and irreversible, death from uremia results with little change in the jaundice. The salvage in this group of patients is increasing with the early and careful use of the artificial kidney when renal shutdown occurs.

Metastatic carcinoma of the liver. Occasionally, a gallbladder is removed because of complaints that have been erroneously attributed to gallstones demonstrated by cholecystogram. The patient's complaints and symptoms have been due to a carcinoma, usually primary in the stomach, intestinal tract, or other intra-abdominal organs. Metastatic tumor in the liver as well as primary tumor may have been overlooked. Jaundice may be caused by impingement on and compression of the ductal system. A

carcinoma of the ductal system or even the gallbladder may grow rapidly and result in jaundice after cholecystectomy. Generally, neoplasia is recognized at the time the gallbladder is removed, and the appearance of jaundice sometime later is anticipated. It is a manifestation of terminal disease and merits no specific measures.

Viral hepatitis. During the past 15 years in a small but increasing number of patients jaundice has developed, believed to be due to viral hepatitis after surgical procedures upon the biliary tract. The jaundice has appeared as early as 5 days and as late as 45 days after operation. In most instances, the patient has received blood or plasma during or shortly after operation. The onset of the jaundice was preceded by general malaise and anorexia. Temperature elevation has been minimal, and there has not been a true leucocytosis. The jaundice has usually been progressive, reaching a bilirubin of 3 to 4 milligrams within from 7 to 10 days after the onset of symptoms. The diagnosis has been based upon an increased cephalin flocculation and thymol turbidity without any other demonstrable cause of the jaundice and the accompanying symptoms. Some patients with viral hepatitis experience only mild symptoms of short duration. Others may run a rapidly fulminating course to end in death. Still others may recover from the acute phase only to suffer later from liver insufficiency.

This type of jaundice may be contracted in other ways and may occur sporadically. Thus it is possible, particularly among young individuals, for it to develop in patients who have been operated upon but to be completely unrelated to anything associated with the surgery performed.

Cholangitis. It is probable that a large proportion of patients with calcareous biliary tract disease have an associated cholangitis. Although this may be present without symptoms, it does tend to flare up when an operative procedure is performed upon the biliary tract. There seems to be some relationship between the mechanical disturbances and the extent of the cholangitis. Thus removal of a gallbladder may cause little increase in the cholangitis, whereas exploration of the common duct and the introduction of radiopaque material to visualize the ductal system may be followed by chills, fever, leucocytosis, and jaundice. A mild degree of jaundice is frequently seen in patients with acute cholecystitis due to cholangitis and unassociated with common duct calculi. After operation, cholecystectomy alone or combined with choledochotomy, the jaundice may increase perceptibly. However, jaundice is rarely profound

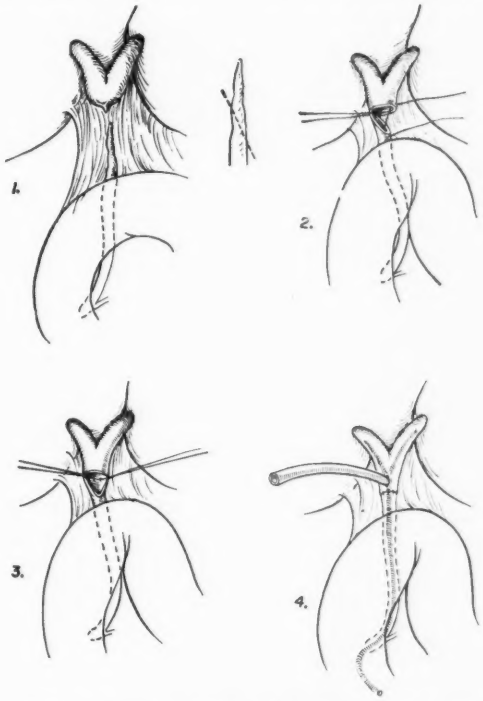

FIG. 3. Repair of stricture due to operative injury. *1,* The injury resulting in complete interruption of continuity of the course of the common bile duct. Small insert shows division of distal segment of common bile duct in oblique fashion. *2,* The ends of the divided common bile duct have been identified and sutures of No. 5–0 silk are placed at opposite ends. *3,* Posterior row of the anastomosis has been completed. *4,* Decompression of ductal system with T tube in place. Distal limb has been extended through the ampulla of Vater into the duodenum.

and tends to clear within from 36 to 72 hours. Penicillin and streptomycin given prior to operation have been of value in preventing acute flagrant exacerbations in patients suspected of having chronic or subacute cholangitis.

Cholangiolitis. From time to time, perhaps once or twice in each 500, operations undertaken for gallbladder disease will reveal a slight enlargement of the liver, a thin-walled gallbladder containing a few calculi, and a common duct that appears smaller than normal in diameter and sometimes edematous. Within a day or two thereafter, the patient becomes jaundiced, the stools acholic. The bilirubin and the alkaline phosphatase become elevated. The temperature may or may not be elevated. As the jaundice increases there is anorexia, general malaise, and gradual weight loss. It may subside spontaneously or it may be progressive. The diagnosis is arrived at by exclusion, being difficult to differentiate from hepatitis due to medications such as chlorpromazine, arsphenamine, cinchophen, and methyltestosterone. This condition of intrahepatic cholangiolitic hepatitis is poorly understood and its cause unknown.

If the jaundice is progressive, operation with exploration and drainage of the common duct should be performed. A biopsy of the liver will establish the diagnosis which has been missed at the first operation. Although the disease may persist and terminate in death, recovery has been reported after prolonged decompression of the common duct.

SUMMARY

Those complications which occur most frequently after operations upon the biliary tract include subhepatic accumulation, hemorrhage, biliary fistulas, bile peritonitis, jaundice, and the recurrences or persistence of symptoms. The causes, clinical manifestations, and management of these are described. An awareness of the complications that may develop after operations upon the biliary tract should prompt the surgeon to employ those measures that are most effectual in their prevention in the preoperative evaluation and preparation of each patient. Emphasis is placed upon meticulousness in identification of anatomic structures so that inadvertent operative injury will not occur.

Jaundice, one of the more serious complications, is often due to obstruction of the ductal system. The causes of obstruction are discussed in order of the frequency with which they have been observed. Calculi, infection, trauma, benign and malignant tumors, foreign bodies, and extrinsic pressure are described relative to their roles.

The trend is toward a decreasing incidence of morbidity of complications and mortality rate. The safety and ease with which surgical therapy is now accomplished in biliary tract disease is dependent upon an appreciation of the factors that keep these at a minimum.

AN EVALUATION OF HOSPITAL INFECTIONS WITH ANALYSIS IN MORTALITY AND MORBIDITY

U. S. Veterans Administration Co-operative Study Committee for Hospital Infections*

THERE IS SAID to be throughout the world an increasingly critical situation involving hospital acquired infections, with bacterial resistance to antibiotics such as penicillin threatening effectiveness of these adjuncts in treatment. Clinical and administrative staffs of hospitals are concerned with complications in patients due to infection with antibiotic resistant organisms, particularly the staphylococcus.

Definition of this problem is necessary as a whole and in individual hospitals, before a baseline can be selected from which to evaluate epidemics or effective controls.

The United States Veterans Administration Division of Research developed a co-operative study to evaluate this problem as it affects selected Veterans Administration hospitals. Two of these are tuberculosis hospitals; one a 150 bed general hospital in a small New England community, another a medium size (500 bed) general hospital in a university city of a quarter million people, and 2 are metropolitan university affiliated general medical and surgical hospitals of 1,000 beds. It is now possible to review the study and some of the data gathered, as well as to present conclusions reached in 18 months of this co-operative effort in 6 hospitals with a total bed complement of 3,320.

REFERENCE LABORATORY

To provide bacteriophage typing and standardize methods of identification of organisms, sensitivity testing and other microbiologic efforts for the entire Co-operative Study, a Central Reference Laboratory was established as an addition to routines of the hospital laboratory at Veterans Administration, Batavia, New York. It has been demonstrated that such a service can easily and economically function, doing an enormous amount of specialized work with the investment of a minimum of additional personnel and facilities (1).

From early returns in the Reference Laboratory it was immediately apparent that indiscriminate use of the various available commercial antibiotic discs led to chaotic results in assaying bacterial sensitivity (2). Even with uniform use of the most reliable commercial discs found by the Reference Laboratory, correlations between the individual hospital laboratories and the Reference Laboratory varied in antibiotic sensitivity tests from 99 per cent with some drugs in certain facilities to 57 per cent with others, the average agreement being 86 per cent. After standardizing discs and utilizing the tube dilution technique as controls, continuing lesser differences were found to be caused by variations in media, incubation time and temperature, amount and age of inoculum, and other technical details. Discrepancies were reconciled by detailed instructions and rare visits to participating laboratories by the Reference Laboratory Chief. On repeated testing since that time correlation of results in antibiotic sensitivity assays averages 99 per cent in the study hospital laboratories and reference laboratory. Examining this further in a series of 13 other uninstructed nonstudy Veterans Administration hospital laboratories correlation in sensitivity tests ranged from 72

*The following individuals participated in the "Antibiotic Resistant Staphylococcus Study": From the Veterans Administration—Dr. Clifford Bachrach, Dr. Max Bovarnick, Dr. William Chardack, Dr. Lewis Griffith, Dr. Wendell Hall, Dr. Gladys Hobby, Dr. Florence Jenney, Dr. Lyndon E. Lee, Jr., Dr. Murray Levin, Mr. Julian Lewis, Dr. Stuart Mudd, Dr. John B. Perkins, Dr. Lloyd Rogers, Dr. Ralph Vogel; in addition, Arnold Branch, Lancaster Hospital, St. John, New Brunswick, Canada; Dr. Maxwell Finland, Thorndike Institute, Boston City Hospital; and Dr. D. Hugh Starkey, Queen Mary Veterans Hospital, Montreal.

TABLE I.—SUSCEPTIBILITY OF ORGANISMS TO ANTIBIOTICS (IN PER CENT)

Degree of susceptibility	*Pen.*	*Tetra*	*Oxy*	*Chlor*	*Amph.*	*Ery.*	*Novo.*	*Strep.*	*Neo.*	*Bacit.*
		Cycline		*C-*	*Antibiotic*					
INFECTION PRIOR TO HOSPITALIZATION (BASED UPON 321 TO 348 CULTURES)										
S.....	24	52	51	50	77	64	87	38	46	50
MR....	9	1	2	2	16	3	12	21	54	49
R.....	67	47	47	47	7	32	1	41	0	1
HOSPITAL ACQUIRED INFECTION (BASED UPON 223 TO 383 CULTURES)										
S.....	7	24	21	21	70	39	73	24	50	57
MR....	3	2	4	4	11	4	26	7	47	41
R.....	90	74	75	75	19	57	1	69	2	2

Based on the first culture isolated from infected patients. Only the cultures of the Staphylococcus aureus, coagulase positive and hemolysin positive, were sufficiently numerous to present. The percentages of the cultures are given which were susceptible (S), moderately resistant (MR), and resistant (R) to the 10 antibiotics.

to 98 per cent with an average of 86 per cent, although two of the laboratories were excluded from these figures and calculations because the results were so far out of range comparison was impossible. In light of the foregoing a reference laboratory is considered essential for standardization and control of reliability in results for such a study, or for valid comparison of data from individual studies.

A noteworthy observation from the Reference Laboratory is that the so-called hospital epidemic strain of staphylococcus, phage type 42B-52-52A-81, is now not the only major pathogenic offender although in 18 months it accounted for 19.3 per cent of the organisms received. A new strain, 47-77-54-53, has been appearing with increasing frequency until it now accounts for 17 per cent of the total cultures received. It is possible that other strains or combinations could develop into major offenders while going unrecognized as such in single hospital laboratories. Recently there has been redesignation of phages with the hospital offender labeled 80-81. This strain 80-81 seems lately to be appearing again in this study with greater frequency. The Reference Laboratory is in a favorable position to distinguish very early this type of invasion and changing general pattern.

Another important function the Reference Laboratory can exercise is the early observation of resistance to various antibiotics. The sensitivities of staphylococci from infections brought to the hospital vary from those of hospital strains (Table I). The pattern of resistance to the various drugs during the course of the study is readily apparent. In the study of susceptibility of organisms to antibiotics Table II is based upon the first culture isolated from infected patients.Only the cultures of the Staphylococcus aureus, coagulase positive and hemolysin positive, were included for presentation. Each table gives the percentage of the cultures which were susceptible (S), moderately resistant (MR), and resistant (R) to the 10 antibiotics. It may appear that in staphylococcus infections acquired both prior to and during hospitalization sensitivity to neomycin and streptomycin is enhanced with time. In truth decreasing use of these two drugs in everyday hospital practice has in effect removed bacteria from sufficient prolonged contact to allow development of resistance. This may imply that there is wisdom in scheduling intervals of enforced removal of selected drugs from clinical use. A time table for such removal would need to be developed for each drug based on the demonstrated interval requisite for locally dominant bacterial strains to develop resistance and, on abstinence from the drug, to reacquire sensitivity. Current sensitivities are now being reported from the Reference Laboratory in a monthly release to study participants.

The resistance to the usual antibiotics of staphylococci found in infections acquired outside the hospital is approaching that of the hospital acquired infections. While the Veterans Hospitals may have selected groups of patients who have been treated in the community and come to the hospital because treatment was ineffective, one may ask how swiftly the reservoir of resistant organisms is building up in the nonhospital community.

When reliable and uniform laboratory information is assured clinical studies may develop in many directions using information thus provided.

DEFINITION OF INFECTION

For the Veterans Administration Co-operative Study, significant and reportable infection was deemed to be any clinical condition which, when cultured by choice of the responsible physician, yielded a pure or predominant staphylococcus culture. Clinically, these ranged from the classical area of inflammatory "heat, redness, tenderness and swelling," through pustules and stitch abscesses, dermatitis and pneumonia to meningitis and septicemia.

REPORTING[1]

To gather data a basic form was developed for reporting each case of staphylococcus infection discovered in participating hospitals during the study interval. This was more detailed than appears requisite for general use, but included some items to permit evaluation of their possible usefulness or significance. In hospitals distinction must be made between what information is desirable and what useful parts of this can be provided without disrupting the institution's true function. While participants in study hospitals continue to use this study form it has been modified for routine reporting of *all* hospital infections, and now includes only those details which appear from experience to be most pertinent and available without taxing unduly those doing the reporting. An additional summary form is used for central reporting.

In practice it was soon apparent that there were wide differences among the various hospitals in what was actually reported. These variations were not reflections solely of difference in opinions as to what constitutes an infection. Even in study hospitals such variations may result from indifference to the importance of infections as a source of contamination for other patients, however minor or asymptomatic they may appear in the hosts.

A review was made of routine prestudy reporting of surgical infections in the group of study hospitals and checked against similar reports during the same interval from nonstudy hospitals. This revealed a frequency of infections in surgical patients ranging from 0.5 to 2.0 per cent averaging about 1.0 per cent. Nonstudy hospitals have continued routine reporting at this level. With initiation of the study the reported frequency of infections in all the participating general medical and surgical hospitals rose to between 4 and 5 per cent, and cases from the medical services were introduced. Improved recognition of cases is considered an immediate tangible benefit of the study.

In one of the large general hospitals where a compulsive and energetic assistant chief of service personally sought all infections in an effort sustained over several months the frequency fluctuated between

[1]The forms mentioned in the following paragraph can be obtained from the United States Veterans Administration Central Office.

TABLE II.—TRENDS IN ALL HOSPITALS—INFECTION PRIOR TO ADMISSION (IN PER CENT)

Degree of susceptibility	Pen.	Cycline: Tetra	Cycline: Oxy	Cycline: Chlor	C-Amph.	Ery.	Novo.	Strep.	Neo.	Bacit.
FROM AUGUST 1957 TO MARCH 7, 1958 (BASED UPON 174 TO 189 CULTURES)										
S.....	28	50	50	50	71	64	87	27	18	52
MR....	11	2	2	3	21	6	12	29	34	17
R.....	62	48	48	47	8	30	1	43	47	31
FROM MARCH 7, 1958 TO SEPTEMBER 8, 1958 (BASED UPON 114 CULTURES EXCEPT FOR OXYTETRACYCLINE AND CHLORTETRACYCLINE WHICH ARE BASED UPON 46 CULTURES)										
S.....	16	48	54	54	78	61	82	43	71	48
MR....	4	0	0	0	12	2	16	7	29	52
R.....	81	52	46	46	10	38	2	49	0	0
FROM SEPTEMBER 8, 1958 TO FEBRUARY 1, 1959 (BASED UPON 100 CULTURES)										
S.....	20	55	—	—	85	64	87	56	83	55
MR....	7	0	—	—	9	1	11	7	17	44
R.....	73	45	—	—	6	35	2	37	0	1
FROM AUGUST 1957 TO MARCH 7, 1958 (BASED UPON 112 TO 200 CULTURES)										
S.....	6	20	21	21	68	49	77	15	36	78
MR....	8	2	3	3	20	5	23	20	61	21
R.....	86	77	76	76	12	46	1	66	4	1
FROM MARCH 7, 1958 TO SEPTEMBER 8, 1958 (BASED UPON 136 CULTURES EXCEPT FOR OXYTETRACYCLINE AND CHLORTETRACYCLINE WHICH ARE BASED UPON 50 CULTURES)										
S.....	11	28	24	24	68	44	71	27	65	51
MR....	3	1	6	4	10	3	28	9	35	49
R.....	86	71	70	72	22	53	1	64	0	1
FROM SEPTEMBER 8, 1958 TO FEBRUARY 1, 1959 (BASED UPON 148 CULTURES)										
S.....	7	28	—	—	73	51	76	28	79	56
MR....	3	1	—	—	9	1	23	7	21	40
R.....	89	71	—	—	18	48	1	64	0	4

TABLE III.—REPORTING OF STAPHYLOCOCCUS INFECTIONS

	Per cent
Monthly surgical reports (1.4 to 2 per cent average)	1
Infection study (GM&S hospitals)	4–5
With effective clinical supervisor	13–15
Absence of supervisor	1
Bed by bed rounds (GM&S hospitals)	10–13

13 and 15 per cent. On his promotion elsewhere it dropped precipitously to the more comfortable prestudy level of 1 to 2 per cent. (Table III).

Stimulated by this occurrence surgical and research staff from the Veterans Administration Central Office co-operating with participants undertook a thorough hospital by hospital, service by service, and bed by bed round of the institutions in the study. Cultures were taken of each actual or clinically suspicious infection, and consultations or pertinent laboratory studies, such as roentgenograms of the chest and hematologic reviews, were obtained. In tuberculosis hospitals, 17.2 per cent of the patient population justified review for the possible presence of bacterial infection other than tuberculosis, while findings in 37 per cent of the patient population in the general medical and surgical hospitals justified study. Patients making up this group fell into two classes: (1) Those whose infection was an incidental finding without obvious influence on cause of hospitalization (examples: indolent varicose or decubitus ulcers, chronic dermatitis, incidental pimples and pustules, granulating burn areas, and sinuses or gangrene in avascular tissues). (2) Those patients whose infection was considered significant in relation to morbidity and hospitalization of the individual. The frequency of significant staphylococcal infections in general medical and surgical hospitals ranged between 10 and 13 per cent. Both groups were considered to be of importance in hospital staff consideration of the problem of infections in that they may serve as a source of environmental contamination and infection of other patients. As is to be expected there was considerable variation in the frequency of infection among patients in wards devoted to various subspecialties. As examples, low rates were found among patients in physical medicine and rehabilitation or ophthalmology, while the frequency was high in the subspecialties of dermatitis, orthopedics, and thoracic surgery.

This survey allows reiteration that:

Reporting of infections is highly variable, requiring understanding and agreement on definition of reportable or significant infections in any service, subspecialty, or patient care institution.

Approximately half of the infections in this study were found on the medical and half on the surgical services.

The frequency of staphylococcus infection may be a fair index of the total spectrum of bacterial infections in a hospital. As might be anticipated the usual bacteria causing infectious diseases in the hospital at any one time include an imposing list. As with staphylococci these are not always the primary reason for hospitalization.

One early and regularly repeated activity of a hospital infection committee might be to obtain indication of the spectrum of bacterial diseases under treatment at stated times. The hospital staff would thus be provided basic information to aid in choice or change of control measures.

FREQUENCY OF INFECTION

From August 1957 through January 1959, i.e., during the 18 months of the Cooperative Study being reported 29,817 patients occupied 3,320 beds in 6 Veterans Administration hospitals. Among them 1,604 staphylococcus cultures were isolated from 1,261 persons, although 47 were taken from personnel in patient contact, and the source of 5 is unknown. One hundred sixteen were recorded as having no clinical staphylococcus infection and resulted from epidemiologic study or other interests. There were 1,093 patients with clinical infections solely or dominantly due to staphylococcus (Table IV).

Approximately half of the 1,093 patients with clinical infection acquired it in the

TABLE IV.—STAPHYLOCOCCUS STUDY—GENERAL CLASSIFICATION OF PATIENTS

Hospital	Bed complement	No. of cultures	Total cases	Source of case: Patients: With clinical infection	Source of case: Patients: Without clinical infection	Source of case: Personnel	Source of case: Not recorded
Tuberculosis							
Batavia	232	46	42	38	0	4	0
Butler	500	49	44	38	2	4	0
GM&S							
Manchester	150	84	74	65	0	7	2
Syracuse	488	217	166	160	4	0	2
Buffalo	950	402	332	317	2	12	1
Brooklyn	1000	806	603	475	108	20	0
Total	3320	1604	1261	1093(.33)	116	47	5

TABLE V.—INFECTION VS. HOSPITALIZATION

Hospital	Beds	Total infections	Prior: No.	Prior: Per cent	In hospital: No.	In hospital: Per cent	Unknown: No.	Unknown: Per cent	No report: No.	No report: Per cent
Tuberculosis 2 Hospitals	732	76	18	24	52	68	1	1	5	7
GM&S	150	65	23	35	19	29	0		23	36
GM&S	488	160	67	42	84	52	1	1	8	5
GM&S 2 Hospitals	1950	792	349	44	356	45	9	1	78	10
Totals	3320	1093	457	42	511	47	11	1	114	10

GM&S—General Medical and Surgical.

hospital, while the other half entered the hospital with the infection already present (Table V). Obviously the problem is not that of hospital-acquired infections alone.

One-third of the 1,093 clinical infections (298) occurred in patients having no manipulation which violated continuity of the skin. One-third of the patients (332) underwent some procedure but suffered the staphylococcus infection elsewhere in the body unrelated to the manipulation. One-third of the staphylococcus infections (329) were at the site of some procedure which interrupted continuity of the integument through anything from venipuncture to surgical incision. In frequency of infections on the major clinical services medicine is as culpable as surgery.

The nature and site of staphylococcal infection is of interest (Table VI). Further information is desirable to determine the degree of severity of infection in certain of those listed. Items under cultures were recorded as clinically significant infections, but the nature of resulting morbidity was not catalogued in the reports. Here again definition is imperative. To illustrate: Among the 39 cases of osteomyelitis only 7 were actual hematogenous infection, while the others were localized and often part of a more general gangrenous process in a digit or extremity, or at sites of trauma, open reductions or wiring. This study does not indicate an increase in primary osteomyelitis.

It is pertinent to record the end results of the staphylococcus infections (Table VII). Chronic infection was recorded if the condition persisted at termination of the hospital stay or for more than 30 days.

One hundred fifty-one patients died among the 1,093 with clinical infection. The nature and sites of infection in deceased patients are indicated in Table VIII. In 63 per cent of these cases the staphylococcus infection was considered to have contributed to death even though it may not have been the primary cause. Of the 95 deaths attributable in some measure to staphylococcus infection, 32 of the infections were present when the patient entered the hospital; 52 were acquired after he entered the institution (Table IX). Among these patients are some in whom staphylococcus infection was the

TABLE VI.—NATURE AND SITE OF STAPHYLOCOCCUS INFECTIONS

	No. of cases
Skin infection	336
Wound infection	180
Pneumonia	124
Pharyngitis	53
Abscess and deep infection	
Perianal	17
Epidural abscess	1
Axillary	2
Other	28
Pilonidal abscess	21
Osteomyelitis	39
Urinary tract infection	39
Urine culture	46
Otitis media	10
Enteritis	9
Septicemia	8
Stool culture	1
Sputum culture	53
Lung culture	9
Nose culture	33
Other	84
Total	1093

TABLE VII.—END RESULTS OF INFECTIONS

	No. of cases
Recovered	608
No residual 543	
With residual 65	
Chronic infection	111
Not stated	223
Deaths	151
Total	1093

terminal event in an otherwise fatal affliction. In 11 cases it is not known whether infection was brought from outside or hospital-acquired.

DISCUSSION

If these figures are any indication of what may be happening in hospitals throughout the country, or in the 171 hospitals of the Veterans Administration alone, they imply a considerable but hardly an alarming portion of hospital effort is in care of hospital-acquired infection.

Due to lack of reliable earlier data, it is impossible to compare present information with prestudy experience in the hope of determining whether all infection is on the increase in frequency, type, severity, or as a cause of death. For such estimates, decision on the basis of clinical impressions would be more dangerous than useful. Such a decision is unnecessary for efforts at solution of the problem in hand.

TABLE VIII.—NATURE AND SITE OF STAPHYLOCOCCUS INFECTIONS IN DECEASED PATIENTS

	No. of cases	*Infections contributed**
Pneumonia	70	58
Wound infection	11	10
Skin infection	15	8
Septicemia	5	4
Urinary tract infection	5	1
Enteritis	3	3
Otitis media	1	0
Pharyngitis	4	1
Cultures		
Urine	3	0
Sputum	9	4
Lung	7	2
Nasal	1	0
Other	17	4
Total	151	95(63%)

*Not necessarily primary cause of death.

TABLE IX.—SUMMARY

	Entering with infections		*Hospital acquired*		
	No.	*Per cent*	*No.*	*Per cent*	*Unknown*
Staphylococcus contributed to death	32	7	52	10	11
Staphylococcus did not contribute to death	16	4	26	5	14
Survivors	409	89	433	85	100
Total (1,093 cases)	457		511		125

Recently, there have been many reminders to all physicians that a readily available partial solution to the problem exists in reapplication in all areas and functions of the hospital of attitudes and disciplines that prevailed as measures against infectious diseases prior to the advent of antibiotic drugs. Real threat exists in persistence of the antibiotic-inspired philosophy that any single instrument, substance, or maneuver can obviate all problems and need for sincere application of an entire program of control measures. The cause or causes of infection problems vary from institution to institution, and from time to time in any one hospital. Housekeeping or laundry may be at fault in one situation, operating suite or surgical dressing techniques in another, while a carrier problem exists in a third. All of these may be operating with additional factors to create difficulty in any hospital. Infection control requires determination of causes and what make up

necessary maneuvers to combat them, attributing to each a correct relative importance and degree of effort. Broad regulations cannot apply.

SUMMARY

Laboratory. In all cases of suspected infection, particularly staphylococcal diseases, it is desirable to confirm the diagnosis by bacteriologic investigation.

Reliable and uniform laboratory information is requisite in clinical studies of infection. In this Veterans Administration study, quality of laboratory information was assured by use of a reference center to establish standards and controls.

Ninety-six to 99 per cent correlation among widely separated laboratories can be maintained in identification of staphylococci, coagulase, and hemolysin as well as assays of antibiotic sensitivity when regulated through a reference laboratory. Without such control correlation is so variable it precludes comparisons of clinical data.

A reference laboratory can distinguish very early changes in types and patterns of infection as well as sensitivity of organisms to treatment.

The reference laboratory is a training area for study hospital staff and general laboratory technicians.

Bacteriophage typing is not necessary or desirable in all infections but should be accessible for study and control of local epidemics.

Clinical. Improved recognition of cases is an immediate and tangible benefit from a study of infections in hospitals.

Reporting of infections is highly variable, requiring understanding and agreement as to definition of reportable and significant infections in any service, subspecialty, or patient care institution.

Bed by bed rounds to identify infected cases are a useful spot check to provide baseline data for assaying the presence of epidemics or the effectiveness of control measures. It is suggested this be one function of a Hospital Infection Committee.

Approximately half of the infections in this study were found on the medical and half on the surgical services. In each about half of the patients entered the hospital with infection, and half were hospital-acquired.

The frequency of staphylococcus infection in a hospital may be a fair index of the total reservoir of all bacterial infections in that hospital.

Infection control in a hospital imposes an administrative obligation entailing professional supervision at a high authoritative level, with intelligent emphasis upon facets and factors determined by objective study and concrete data to be contributing to the individual hospital or service problem.

No single instrument, substance, or maneuver can obviate infection or the need for sincere application of an entire program of control measures. The program must be developed with emphasis in correct relative proportion on phases of the problem specific to each institution.

CONCLUSION

Staphylococcus infection is a community problem. Badly needed is agreement on terms and analysis of limitations in techniques. For their application in hospitals uniformity is requisite, and one must untangle return to asepsis from results due to other control measures. Education becomes necessary in accomplishing these things; education as to uniformity in terms and techniques with their known limitations, but above all re-education as to the dignity of honesty in recognizing, assessing, and reporting difficulties.

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A STUDY OF THE DEVELOPMENT AND STRUCTURAL RELATIONSHIPS OF THE TESTIS AND GUBERNACULUM

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A STEP BY STEP INVESTIGATION of the development of the testis and its gubernaculum provides a body of data from which the significance of the morphology and topography of the organ becomes apparent. Only by such a study can one obtain a basis for a satisfactory assessment of the variations and abnormalities that are often met with in these structures. A detailed knowledge of the development of the testis is also of interest because there is a gap between the well recognized early stages and the mature organ together with its relationship to other organs or structures. This study is presented in order to clarify certain aspects of the structural relationships of the testis and to discuss the structure of the gubernaculum at different phases in testicular development.

HISTORICAL

In the past 200 years, several studies have been made of the testis and its descent. Galen and Vesalius were acquainted with cases showing abnormal positions of the testis. Vesalius is credited with being the first person to describe the processus vaginalis testis proprius. Haller, Camper, and John Hunter were among the earliest investigators who published papers on testicular descent. In 1786, John Hunter published an extensive work on the testis and presented excellent illustrations of the testis and its structural relationships. Among the recent investigators are Bramann, Lockwood, Frankl (4, 5), Felix, and Hart.

MATERIAL AND METHOD

Thirty-one specimens of human embryos were studied. They ranged from 5 weeks of age to term. The preserved embryos were dissected under water, unstained, with or without the aid of a dissecting microscope. Histologic studies were made on the collection of slides in the embryologic collection in the Department of Anatomy of the University of Michigan, School of Medicine. Table I gives a brief summary of the different specimens studies.

From the Department of Anatomy, School of Medicine, University of Michigan, Ann Arbor.

DEVELOPMENTAL STUDY

Origin of testis. The germ cells are first noted in the yolk sac of human embryos of 3 millimeter crown-rump length. The germ cells subsequently migrate from this position through the dorsal mesentery into the genital fold over the mesonephros.

By the 14 to 16 millimeter crown-rump length stage (about 7 weeks of gestation), the gonad has differentiated into the testis or the ovary.

There are two theories as to the origin of the seminiferous tubules. According to Wilson and Gilman the seminiferous tubules develop from primary sex cords while the interstitial cells arise from the mesenchyme of the gonadial ridge. On the other hand, Gruenwald maintains that the seminiferous tubules develop "from the original gonad blastema either by way of the gonadic cords or from the mesenchymal stroma of the organ."

The rete cords first appear in the 10 millimeter embryos and become progressively more complex by anastomosing freely. By the stage of 100 millimeter crown-rump length (about 14 weeks of age), they become tubular in form; they unite with the vasa efferentia before birth.

Early and prenatal position of the testis. The interrelationships of the urinary and the

genital systems make it necessary to review the highlights in the development of the urinary system.

In the human embryo, the pronephros begins to appear in embryos of 9 to 10 somites, or about 3 weeks of age. The pronephros develops retroperitoneally and it is soon replaced by the mesonephros which will be discussed in greater detail. Pronephric tubules appear late in the third week and they meet, unite, and extend caudally to form the pronephric duct.

In the 10 millimeter embryo (about 5 weeks of gestation), the mesonephros has replaced the pronephros and incorporated the pronephric duct which is now to be referred to as the mesonephric duct. The greatest extent of the mesonephros is from the second thoracic vertebral segment to the second lumbar vertebral segment. The fold of parietal peritoneum over the mesonephros has a maximal extent from the fourth cervical vertebral segment to the fourth lumbar vertebral segment. This mesonephric fold covers the ventral aspect of the mesonephros and attaches the organ by a broad base to the dorsal body wall.

The formation of mesonephric tubules begins in the cephalic pole of the mesonephros and extension of tubule formation caudad in sequence along with tubular degeneration cephalad. Toward the end of the seventh week of gestation (20 to 22 mm. C.R.L.) the mesonephros attains its greatest bulk and thereby pushes its peritoneal covering into the abdominal cavity. The mesonephros does not occupy the entire length of the mesonephric fold. The cranial portion of the mesonephric fold extending from the mesonephros to the pleuroperitoneal fold can be called the diaphragmatic fold of the mesonephros.

By the fourth week (5 mm. embryo C.R.L.) the genital fold (parietal peritoneum on the ventral surface of the germ cells which migrated to and congregated upon the mesonephros) extends from the fifth or sixth thoracic vertebral segment to the tenth thoracic vertebral segment. In the 7 millimeter embryo (about the end of the fourth week of age) two grooves appear on the medial and lateral sides of the gonad and separate it from the mesonephros. The grooves progressively deepen until the gonad is essentially suspended from the mesonephros by a relatively narrow mesorchium (Fig. 5a).

TABLE I.—EMBRYOS AND SLIDES

E.H.	*C.R. Length, mm.*	*Age, weeks*	*Remarks*
56	10	5	Slide. Microscopic analysis of the gubernaculum
453	17	6 2/7	Slide. Microscopic analysis of the gubernaculum
563	22	7	Gross dissection for measurements of testis and gubernaculum
164	24	7 2/7	Slide. Microscopic analysis
843	26.5	7 5/7	Gross dissection for measurements of testis and gubernaculum
156	30	8	Slide. Microscopic analysis
515	32	8 1/7	Gross dissection. Measurements
785	35	8 1/7	Slide. Microscopic study
487b	37	8 5/7	Gross dissection. Illustration and measurements
17p	39	9	Slide. Microscopic study
561	42	9 2/7	Gross dissection. Measurements
535	51	9 6/7	Gross dissection. Measurements
370a	53	10	Slide. Microscopic analysis
554	56	10 4/7	Gross dissection. Illustration and measurements
471	63	11	Gross dissection. Measurements
208	77	12 1/7	Gross dissection. Measurements
320	90	12 6/7	Gross dissection. Measurements
209	91	13 1/7	Gross dissection. Measurements
891	97	14	Gross dissection. Illustration and measurements
182	99	13 4/7	Gross dissection. Measurements
145L	104	14 2/7	Slide. Microscopic study
364a	115	15	Slide. Microscopic analysis of the gubernaculum
332	120	15 5/7	Gross dissection. Measurements
210	145	17 1/7	Gross dissection. Measurements
30	145	17 1/7	Slide. Microscopic analysis
532	155	17 6/7	Gross dissection. Measurements
518	160	18 4/7	Gross dissection. Measurements
31	180	20 3/7	Slide. Microscopic analysis
593	185	20 5/7	Gross dissection. Measurements
747	225	27 3/7	Gross dissection. Illustration and measurements
923	380	39 2/7	Slide. Microscopic analysis of the gubernaculum

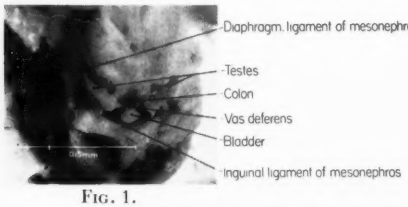


FIG. 1.

FIG. 2.

FIG. 1. Gross dissection of 37 millimeter embryo (beginning of ninth week) illustrating the intraperitoneal position of the testis, the diaphragmatic ligament, and the inguinal ligament of the mesonephros.

FIG. 2. Gross dissection of 56 millimeter embryo (eleventh week) showing the relationships of the plica vascularis, the diaphragmatic ligament of the mesonephros, the vas deferens, the inguinal ligament of the mesonephros, and the processus vaginalis.

Since the gonad does not occupy the entire extent of the mesonephros, the mesonephric fold presents these parts: (1) the pregonadal portion which is cephalic to the cranial tip of the testis; (2) the gonadal portion which lies dorsal to the main bulk of the testis; and (3) the postgonadal portion which extends to the cloacal region and is caudal to the distal tip of the testis. These various parts of the mesonephric fold project into the abdominal cavity. As the mesonephric tissue degenerates, it forms strands of connective tissue and residual mesonephric tissue. In the pregonadal area this strand may be called the diaphragmatic ligament of the mesonephros; it lies within the diaphragmatic fold of the mesonephros (Fig. 2).

In an embryo of 56 millimeter crown-rump length (tenth week), the testicular vessels have developed, arising from the aorta at about the first lumbar vertebral level. Although Lockwood refers to the diaphragmatic ligament of the mesonephros as the plica vascularis since he believes that the ligament becomes the peritoneal fold over the testicular vessels, the plica vascularis (i.e., the peritoneal fold over the testicular vessels) and the diaphragmatic ligament of the mesonephros can be seen clearly by the tenth week (Fig. 2). It thus seems clear that the plica vascularis should be considered as distinct from the diaphragmatic ligament of the mesonephros. By the thirteenth week (90 mm. embryo C.R.L.) the diaphragmatic ligament has disappeared.

With degeneration of the mesonephros the gonadal part of the mesonephric fold becomes thinner to such a degree that it can be considered to be the body wall part of the mesorchium (Fig. 5b). Because of the close proximity of the testis to the mesonephric tubules, some of the tubules become connected with the rete cords and the mesonephric duct becomes the passage for sex cells. The mesonephric tubules cephalad to the testis regress and remnants are often encountered as the appendix of the epididymis. The ductuli efferentes or vasa efferentia are the mesonephric tubules which unite with the rete cords. The ductuli efferentes lead into the ductus epididymidis which is the proximal convoluted portion of the mesonephric duct. The ductuli efferentes and the ductus epididymidis collectively are referred to as the epididymis. The ductus deferens is the distal portion of the mesonephric duct which after reinforcement with smooth muscle empties through the ejaculatory duct into the urethra. The mesonephric tubules below the level of the testis form the paradidymis.

The testis at 7 weeks of age (about a 20 mm. C.R.L. embryo) is thus suspended from the mesonephros by the mesorchium.

With degeneration of the gonadal portion of the mesonephros, the mesorchium which attaches the testis to the mesonephros can be regarded as having been lengthened by the thinning of the mesonephric fold. This mesorchium contains the epididymis, the ductus deferens, the paradidymis, the appendix of the epididymis, and dense strands of connective tissue. It provides the pathway through which blood vessels reach the testis. The strands of young connective tissue within the mesorchium and within the testis proper blend with the cephalic portion of the mesenchymatous tissue within the postgonadal portion of the mesonephric fold. The degeneration of the mesonephros and the suspension of the testis from the dorsal abdominal wall cause the testis to become an intraperitoneal organ. Gross dissection of a 37 millimeter embryo (at the beginning of the ninth week) illustrates this statement (Fig. 1).

Gross dissection of a 22 millimeter embryo (about seventh week of gestation) reveals the postgonadal fold of the mesonephros (which can be called the inguinal fold of the mesonephros) extending from the distal tip of the gonad to the anterior abdominal wall at the level of the fourth lumbar vertebral level. Medial and slightly dorsal to the caudal end of the mesonephros is the mesonephric duct (vas deferens) curving medially and ventrally toward the posterior aspect of the bladder. This basic relationship persists until the time the testis descends into the scrotum (at about the twenty-eighth week or just before birth) with some quantitative changes at the region of the inguinal fold of the mesonephros. The caudal tip of the mesonephros within the inguinal fold of the mesonephros reaches the anterior abdominal wall prior to the differentiation of the abdominal musculature which can be first identified in an 11 millimeter embryo (about 5 weeks of gestation). With the degeneration of the postgonadal mesonephros, there is developed the inguinal ligament of the mesonephros which lies within the inguinal fold as did

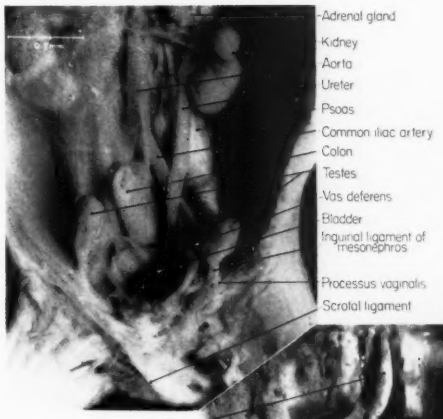


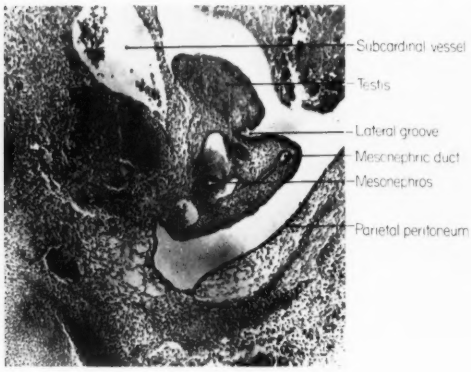
FIG. 3.

FIG. 4.

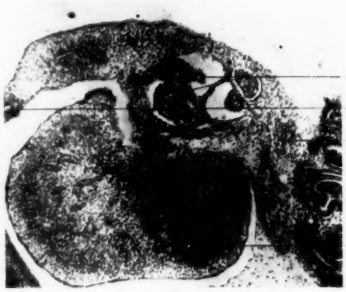
FIG. 3. Gross dissection of 97 millimeter embryo (fourteenth week) demonstrating the scrotal ligament. At the caudal end it fans out attaching to the pubic tubercle and crest, the connective tissue at the root of the penis, the membranous layer of the subcutaneous connective tissue of the perineum, and the fascia lata of the femoral triangle.

FIG. 4. Gross dissection of 225 millimeter embryo (about twenty-eighth week of gestation) showing the processus vaginalis as a sac extending to the external abdominal oblique aponeurosis lying ventral to the inguinal ligament of the mesonephros.

the diaphragmatic ligament. By the beginning of the ninth week (37 mm. C.R.L.) the inguinal ligament can be demonstrated in a gross dissection (Fig. 1). The inguinal ligament of the mesonephros extends into dense mesenchymatous tissue in the region of the future external abdominal aponeurosis. When the abdominal musculature begins to differentiate, it surrounds the inguinal ligament of the mesonephros. The transversus abdominis muscle is completely interrupted. However, the internal abdominal



a



b

FIG. 5. a, Cross section of 17 millimeter em[illegible]o × 42 (EH 453), showing grooves of the testis. b, [illegible]nsverse section of 24 millimeter embryo, × 42 (EH 164 [illegible]showing degenerating mesonephros, mesorchium, and [illegible]traperitoneal testis.

oblique muscle layer, in spite of being pierced by the inguinal ligament, gives off skeletal fiber bundles which surround and blend with the inguinal ligament of the mesonephros (Fig. 6a).

The scrotum. Spaulding states that the genital swellings become distinguishable in the 19 millimeter human embryo (early seventh week of age). By the stage of 24 millimeter crown-rump length one can see microscopically a condensation of the mesenchymal cells of the genital fold. The cephalic end of this ligament attaches to the external abdominal aponeurosis directly opposite the attachment of the inguinal ligament of the mesonephros. Its caudal end blends with the subcutaneous mesenchymal condensation of the genital fold. The genital fold will become the scrotum; therefore, this ligament is called the scrotal ligament.

By gross dissection of an embryo of 97 millimeter crown-rump length (fourteenth week) one can demonstrate the scrotal ligament clearly. At the caudal end it fans out attaching to the pubic tubercle and crest, the connective tissue at the root of the penis, the membranous layer (Colles' fascia) of subcutaneous connective tissue of the perineum, and the fascia lata of the femoral triangle. This relationship agrees with the reported findings of Lockwood, Felix, Moszkowicz, and Wyndham; it is in contradiction with the results of Bramann, K[illegible]ratsch, Frankl (5), R. Hunter, Forssner, and Wells. Thus, although the testis is suspended by a mesorchium within the peritoneal cavity, it is connected to the membranous layer (tunica dartos scroti) of the scrotal fold by a continuous ligamentous structure, the gubernaculum testis, composed of the inguinal ligament of the mesonephros and the scrotal ligament (Fig. 3).

The processus vaginalis. The processus vaginalis was first noted in an embryo of 22 millimeter crown-rump length as a dimple on the ventral aspect of the inguinal ligament which gradually becomes deeper and larger in diameter. In the 37 millimeter embryo (Fig. 1) the processus vaginalis begins as a dimple ventral to the attachment of the inguinal ligament of the mesonephros to the ventral abdominal wall. By the ninth week (40 mm. C.R.L.) the position and appearance of the processus vaginalis are very clear. An embryo of 56 millimeter crown-rump length (eleventh week of age, Fig. 2) shows the relationships of the plica vascularis, the diaphragmatic ligament of the mesonephros, the vas deferens, the inguinal ligament of the mesonephros, and the processus vaginalis. By the stage of 225 millimeter embryo (about twenty-eighth week of gestation) it is a sac extending to the external abdominal oblique aponeurosis lying ventral to the inguinal ligament of the mesonephros (Fig. 4)

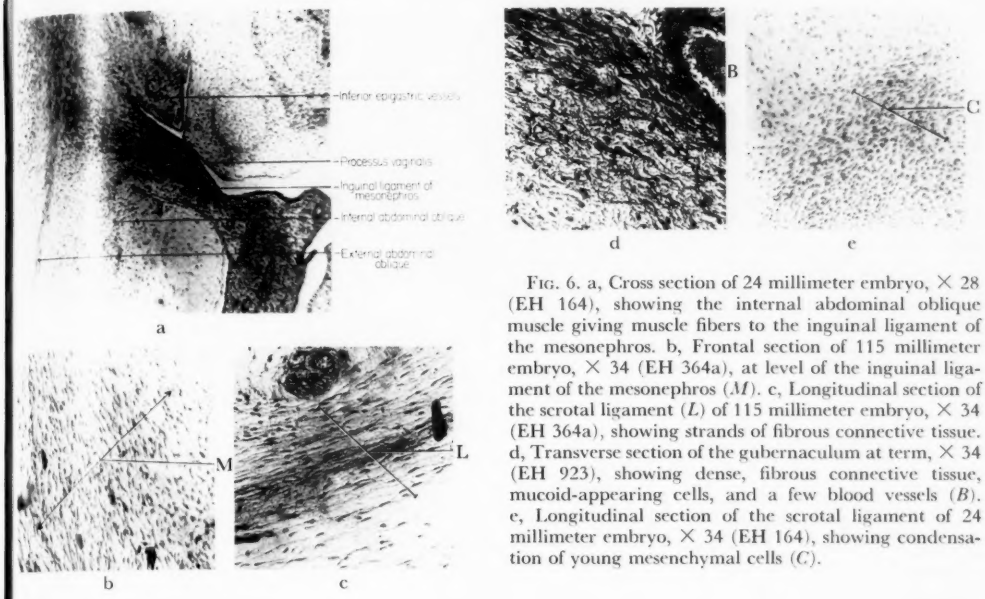


FIG. 6. a, Cross section of 24 millimeter embryo, × 28 (EH 164), showing the internal abdominal oblique muscle giving muscle fibers to the inguinal ligament of the mesonephros. b, Frontal section of 115 millimeter embryo, × 34 (EH 364a), at level of the inguinal ligament of the mesonephros (*M*). c, Longitudinal section of the scrotal ligament (*L*) of 115 millimeter embryo, × 34 (EH 364a), showing strands of fibrous connective tissue. d, Transverse section of the gubernaculum at term, × 34 (EH 923), showing dense, fibrous connective tissue, mucoid-appearing cells, and a few blood vessels (*B*). e, Longitudinal section of the scrotal ligament of 24 millimeter embryo, × 34 (EH 164), showing condensation of young mesenchymal cells (*C*).

It forms an invaginated serous covering of the inguinal ligament. In a cross section of the inguinal ligament, the processus vaginalis forms a crescentric sac over the ventral aspect of the inguinal ligament. Cranially the line of reflection between the parietal and visceral mesentery-like suspension is closer together, but distally it is more widely separated.

STRUCTURAL RELATIONSHIP

Prenatally, the testis occupies a position comparable to the ovary. Above, the testis is bounded by the bifurcation of the common iliac vessels and below by the inguinal ligament. Dorsally and slightly inferior to the testis lies the inguinal ligament of the mesonephros.

From the hilus of the testis, the vas deferens runs medialward to the back of the bladder crossing the umbilical (internal iliac) artery and ureter on their anterior aspect. The vas deferens receives a vascular twig from the umbilical artery as it crosses at the vessel.

The vascular supply of the testis is by way of the testicular artery which arises from the abdominal aorta below the renal artery. The testicular artery runs retroperitoneally to the epididymis and testis. It crosses the ureter and gives a twig to it. The testicular vein on the left empties into the renal vein while on the right side, it is a tributary of the inferior vena cava.

The inferior epigastric artery (a branch of the external iliac artery) lies just medial to the inguinal ligament of the mesonephros to which it sends a twig.

DESCENT OF THE TESTIS

Quantitative data. Although from the study of these specimens no conclusions can be drawn as to the causative factors in the descent of the testis and the role of the gubernaculum in this phenomenon, it seemed worthwhile to make quantitative measurements of the structures involved. Table II presents the quantitative data.

Often one finds statements that the gubernaculum "shortens relative to the whole body." A graph of the length of the entire gubernaculum, as well as of the inguinal ligament of the mesonephros and the scrotal ligament (Fig. 7), shows strikingly that the

TABLE II.—DIMENSIONS OF TESTIS AND GUBERNACULUM AT VARIOUS AGES

	Testis, mm.		*Gubernaculum, mm.*			
C.R.L.	*Length*	*Average diameter*	*Length of ing. lig. meso.*	*Greatest diameter of ing. lig. meso.*	*Per cent of I.L.M. length to diameter*	*Length*
22	3.4	0.6	0.5	<0.1	?	0.5
26.5	3.6	0.6	0.6	<0.1	?	0.6
32	3.2	0.8	0.8	0.1	12.8	0.8
37	2.8	0.8	0.8	0.1	12.5	1.3
42	2.8	1.1	0.9	0.2	22.2	1.9
51	3.1	1.0	1.1	0.4	36.3	3.7
56	2.9	1.4	1.3	0.5	38.4	4.7
63	3.8	1.6	1.4	0.5	35.7	4.9
77	3.7	1.6	2.8	0.8	28.5	6.8
90	3.4	1.9	3.0	1.0	33.3	8.0
91	4.5	2.1	3.2	1.2	37.5	7.6
97	4.5	2.1	3.5	1.3	37.1	8.5
99	3.3	2.0	3.5	0.9	25.7	9.8
120	5.0	2.3	4.7	1.2	25.5	12.3
130	5.4	2.5	5.5	1.6	29.0	15.1
140	5.7	2.5	7.1	1.9	26.7	16.0
155	5.8	2.6	8.7	2.2	25.3	17.4
185	7.3	4.3	12.1	2.7	22.3	22.0
225	7.9	5.3	14.0	4.6	32.8	33.8

gubernaculum does not shorten relative to the whole body. Rather, the length of the gubernaculum up to the time of its final descent into the scrotum increases relatively faster than does the body as a whole. The fact that the gubernaculum increases in length relatively faster than does the crown—rump length of the embryo stands in contrast to the length of the testis, which during this period from the seventh to the twenty-eighth week, increases linearly with respect to the body length.

The inguinal ligament of the mesonephros becomes relatively and progressively more slender up to the 185 millimeter stage; its greatest diameter being 12 per cent at 32 millimeters and only 22 per cent at 185 millimeters (Table II). The increase in relative thickness of the gubernaculum at the 225 millimeter stage is in agreement with the findings of Wyndham who reported that at about the 20 centimeter stage, the gubernaculum becomes greatly enlarged.

The final descent of the testis occurs at the beginning of the twenty-ninth week of age. During the descent of the testis, the abdominal musculature evaginates; thus contributing coverings for the testis and its associated structures. The innermost covering of the testis is the tunica vaginalis testis comprised of visceral and parietal layers. The visceral layer is the original peritoneal covering of the testis prior to its descent while the parietal layer is the wall of the processus vaginalis. The next covering is the internal spermatic fascia (contributed to by the transversalis fascia of the abdominal cavity).

The internal abdominal oblique muscle gives rise to the cremasteric muscle and fascia which envelop the testis like a sling and function to raise or lower the gland. The external spermatic fascia is derived from the aponeurosis of the external abdominal oblique muscle. The last specialized covering of the testis and its associated organs is the tunica dartos scroti which is continuous above with the membranous and fatty layers of the subcutaneous tissue of the anterior abdominal wall and below with the membranous layer (Colles's fascia) and fatty layer of the perineum. This is the basic relationship seen in the descended testis (Fig. 8).

MICROSCOPIC ANALYSIS OF THE GUBERNACULUM TESTIS

Since the gubernaculum testis is composed of two parts, the inguinal ligament of the mesonephros and the scrotal ligament, histologic study of the structures will illustrate the changes noted in the organ. In a

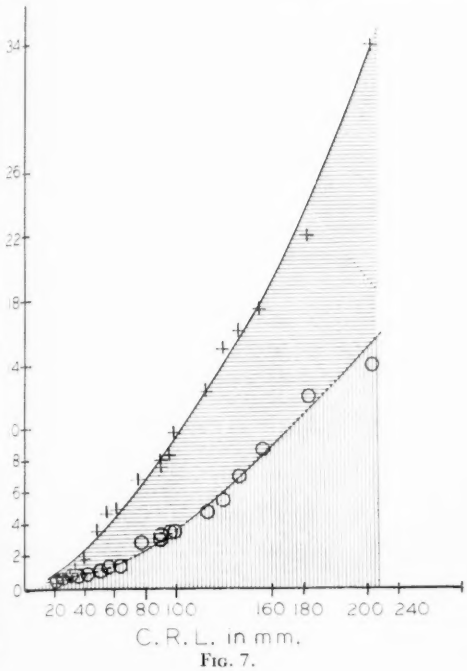


FIG. 7.

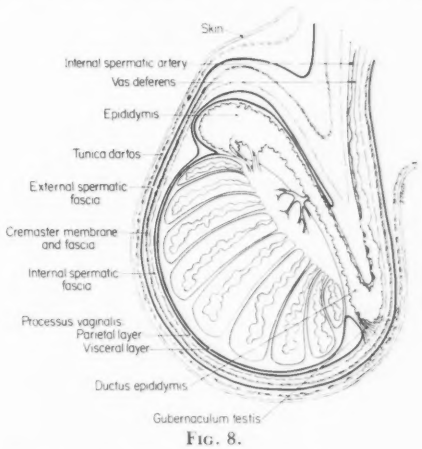


FIG. 8.

FIG. 7. Graph showing relationship of components of gubernaculum testis in embryos of varying sizes. Horizontal hatching represents length of scrotal ligament. Vertical hatching represents length of inguinal ligament of mesonephros. o, Length of inguinal ligament of mesonephros. +, Length of gubernaculum.

FIG. 8. Schematic representation of the descended testis and its coverings.

24 millimeter embryo (eighth week) a cross section through the inguinal ligament of the mesonephros shows rich vascular network, young mesenchymal cells, mesonephric tubules and glomeruli, intrinsic smooth muscle fibers and skeletal muscle fibers—appropriated from the internal abdominal oblique muscle (Fig. 6a). By the fifteenth week of age (115 mm. embryo) the inguinal ligament of the mesonephros has lost some of its vascularity and there are few remnants of mesonephric tubules and glomeruli. The mesenchymal cells are, by this stage, more abundant and there is an increase in the smooth muscle and skeletal muscle fibers (Fig. 6b). The scrotal ligament changes from a condensation of young mesenchymal cells in a 24 millimeter embryo (Fig. 6e) to moderately dense strands of fibrous connective tissue in a 115 millimeter embryo (Fig. 6c). In the term fetus, it consists of dense, fibrous, connective tissue and mucoid-appearing cells as illustrated in Figure 6d.

SUMMARY

1. The development of the testis begins retroperitoneally, but with growth of the testis and degeneration of the mesonephros, the testis becomes an intraperitoneal organ; it is then completely peritonealized and possesses a mesorchium through which vessels and nerves reach it.

2. The gubernaculum is composed of two essential parts: (a) the inguinal ligament of the mesonephros; and (b) the scrotal ligament.

3. The gubernaculum testis is attached superiorly to the proximal tip of the vas deferens and distally to: (a) the pubic tubercle and crest, (b) the fascia lata in the femoral triangle, (c) the inguinal ligament, (d) the membranous layer of subcutaneous connective tissue (Colles' fascia) of the perineum, and (e) the tunica dartos scroti.

4. The largest strand of the gubernaculum testis goes to the scrotum.

5. Microscopically, the gubernaculum testis is composed of: (a) a rich vascular net-

work, (b) young and dense mesenchymal cells, (c) intrinsic smooth muscle fibers, (d) skeletal muscle fibers contributed to by the internal abdominal oblique muscle, and (e) dense, loose, and mucoid connective tissue.

6. All the aforesaid components of the gubernaculum testis are not seen at every age.

7. The intraperitoneal position of the testis and its anatomic relationship to adjacent structures are discussed.

8. Up to the time of descent of the testis into the scrotum, the lengths of both the scrotal ligament and the inguinal ligament of the mesonephros are found to increase more rapidly than the crown-rump length of the embryo or the length of the testis itself.

9. The anatomic position of the finally descended testis and its coverings derived from the abdominal musculature and the subcutaneous tissue of the genital fold are described.

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ELECTIVE EXTRAPERITONEAL CESAREAN SECTION

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ELECTIVE extraperitoneal cesarean section greatly increases the safety of operative delivery and eliminates the usual postoperative complications and discomforts. The elective use of the procedure is usually reserved for demonstrations and teaching purposes. Ordinarily, the primary application of the principle of the extraperitoneal approach to the lower uterine segment has been in cases of overwhelming uterine infection. The indications for the operation have been extended recently to include those obstetric cases in which there is potential, if not actual, infection—in spite of the widespread use of antibiotics in modern obstetrics. This study is presented to indicate the need and the value of the extraperitoneal cesarean section as an elective procedure. This is a definite departure from the usual role of the operation in the face of severe intrauterine infection during labor.

The extraperitoneal cesarean section is an old operation, performed by the progressive surgeons of the 1800 and 1900's in an effort to reduce the impossibly high maternal mortality from infection at the time of cesarean section. The prevention of gross contamination of the peritoneal cavity, therefore, has been the goal and success of the procedure. The use of antibiotics, while reducing the complications of infection in obstetrics immeasurably, has not entirely removed the risk of such infections from various obstetric operative procedures. There are those infections which do not respond well to antibiotic therapy and there are increasing numbers of patients who cannot tolerate the antibiotic agents or who rapidly become sensitized to them. Intraperitoneal contamination must remain a matter for concern, despite limited spill at the time of classical or low cervical cesarean section, even though modern antibiotic therapy is utilized. There is, therefore, a definite need for an extraperitoneal procedure beyond mere academic interest. Many other postoperative complications are obviated by not entering the peritoneal cavity.

Spillage of amniotic fluid and large quantities of blood, both clotted and unclotted, is insulting to the peritoneum, even when these fluids are not contaminated. The elective extraperitoneal cesarean section is proposed, then, not only for primary elective operative cases, but also for repeated cesarean sections.

In no instance has labor been involved in the following cases. The indications in 48 primary cases were: placenta previa with hemorrhage in 5, placenta abruptio in 7, absolute pelvic contraction in 7, previous obstetrical disaster in 4, previous extensive vaginal repair in 3, prolapsed cord with living child in 3, breech presentation in elderly primipara in 3, severe psychosis in 4, severe diabetes mellitus in 4, hydrocephalic infant in 2, coma with high fever in 1, and pelvic tumor in 5. The indications in the 77 secondary cases were: first repeat or second cesarean section in 62, second repeat or third cesarean section in 12, third repeat or fourth cesarean section in 2, and fourth repeat or fifth cesarean section in the final patient.

In each of these indications, the decision that a trial of labor would not be permitted was made on clinical considerations and circumstances existing at the time of each obstetric situation. The placental accidents were all accompanied by severe hem-

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FIG. 1. *A*, Properitoneal fat overlying the parietal peritoneum. *B*, The lower uterine segment with the presenting fetal part. *C*, The bladder and its left lateral edge. *D*, The fine layer of fascia overlying the lower uterine segment. *E*, The obliterated hypogastric artery. *F*, The large dilated vessels and fat along the lateral border of the uterus.

orrhage without onset of labor in the presence of an uneffaced and undilated cervix. The psychotics were operated upon at the behest of psychiatric consultants. The repeat cesarean sections were done in accordance with the concept: "Once a section, always a section." The operations effected for hydrocephalus of the infant involved religious precepts of a philosophic nature with aversion to damage to the fetus. The patient in a coma of unknown cause was operated upon on the eighty-fifth day of coma and the third day of a fever of over 106 degrees F. The patients with pelvic tumors or who were to have tubal ligation were operated upon by the extraperitoneal approach with the knowledge that immediately after cesarean section the peritoneal cavity would be entered for removal of the neoplasms or for tubal ligation in a clear field.

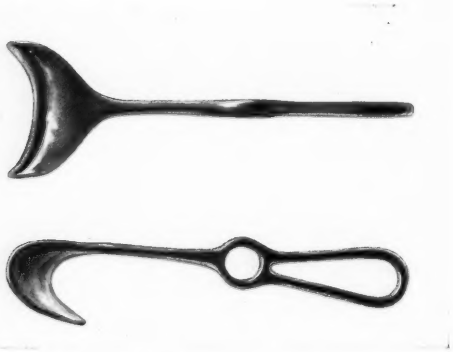

FIG. 2. Fritsch retractor, anterior and lateral views.

METHOD

The technique employed is discussed in detail to emphasize those points which made this modification of the Norton technique feasible and to describe the importance of detail and anatomy.

1. A transverse abdominal incision is made.

2. The fascial incision is carried laterally approximately 4 centimeters beyond the outside border of the rectus muscle on both sides.

3. The recti are separated from the fascia forward to the pubis and approximately 6 centimeters toward the umbilicus.

4. The recti are then separated from the peritoneum and bladder inferiorly throughout the extent of the dissection.

This wide dissection under the skin provides sufficient space for the removal of the child, making a difficult operation considerably easier.

5. The area to the left of the bladder is explored by blunt dissection and the space of Bogros is exposed.

6. The following anatomic landmarks are now identified (Fig. 1): (a) properitoneal fat overlying the parietal peritoneum; (b) the lower uterine segment with the presenting fetal part; (c) the bladder and its left lateral edge; (d) the fine layer of fascia overlying the lower uterine segment; (e) the obliterated hypogastric artery; (f) the large dilated vessels and fat along the lateral border of the uterus.

7. In this dissection, the obliterated hypogastric artery often is pulled cephalad with the peritoneal fold. In the original Norton procedure, the obliterated hypogastric vessel was pulled toward the midline with the

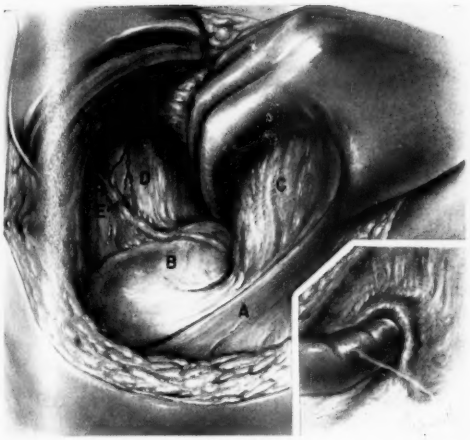

FIG. 3.

FIG. 4.

FIG. 3. The bladder is now gently retracted medially with the fingers. *A*, Parietal peritoneum. *B*, Posterior peritoneal fold. *C*, Bladder. *D*, Lower uterine segment. *E*, Obliterated hypogastric artery. *F*, Fatty tissue and large vessels in the lateral pelvic space. Inset, Method of dissecting with finger-tip.

FIG. 4. Further progression in the blunt dissection of the area. *A*, Parietal peritoneum. *B*, Posterior peritoneal fold. *C*, Bladder retracted laterally. *D*, Lower uterine segment. *E*, Obliterated hypogastric artery. *F*, Fatty tissue and large vessels in the lateral pelvic space.

bladder. This variation in technique yields three fundamental advantages: (a) protection of the thin peritoneum; (b) protection of the left lateral uterine vessels; (c) improved anatomic exposure of the uterine fascia.

This latter point is especially important in those instances when there is a low-lying peritoneal fold, and is particularly helpful in the elective operation in which there has been no labor to thin out the tissues of this area. The process of labor pulls the peritoneal fold cephalad as the lower segment thins and expands. This usually is not apparent in the elective situation.

8. Proper retraction of the recti and anterior abdominal wall fascia and skin bilaterally is most important at this point.

The Fritsch retractor is ideal (Fig. 2). It is wide, curved, and has a deep, flat lip. The intelligent use of this retractor throughout the operation by both surgeon and assistant makes the execution of the procedure much easier.

9. The bladder is now gently retracted medially with the fingers (Fig. 3). It is advanced toward the right side and teased from the superficial fascia of the lower uterine segment. At this time, the bladder is separated from the parietal peritoneum. Division of the urachus at this point often facilitates this part of the dissection. The peritoneal fold is freed from the posterior vesical wall almost entirely by blunt dissection. There is a great deal of variation in the way this step can be accomplished and care must be taken not to perforate either the bladder wall or the peritoneum with the fingers (Fig. 4). Sharp dissection is not recommended because it increases these possibilities.

10. The bladder is retracted to the right side and a small, very superficial incision is made transversely in the fascia overlying the lower uterine segment (Fig. 5). This is then extended laterally in both directions providing space for insertion of the retractor blade under it, making a wider dissection (Fig. 6). The bladder and peritoneum are now superior to the tissue plane.

This is the most important step, since it furnishes excellent protection for the bladder

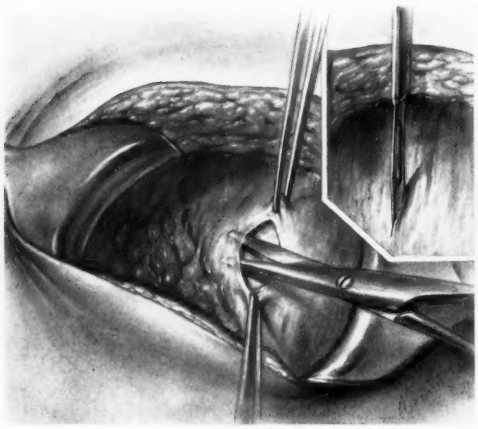

FIG. 5.

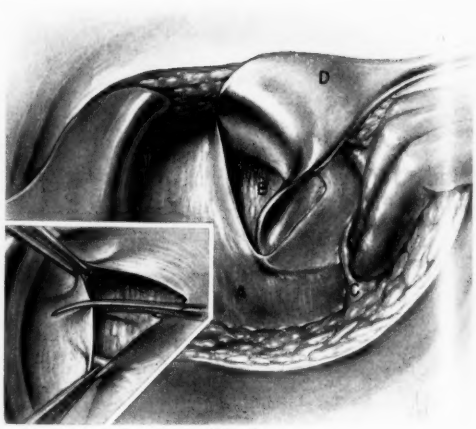

FIG. 6.

FIG. 5. Inset, Method of making an incision in the superficial uterine fascia. Main illustration, Method of enlarging the fascial incision with a curved scissor.

FIG. 6. Inset, Method of extending the fascial incision. Main illustration, Extension of the fascial dissection utilizing the Fritsch retractor. Shows the next step in extension of the dissection enlarging the operative field. *A*, Superficial uterine fascia. *B*, Lower uterine segment. *C*, Edge of posterior peritoneal fold. *D*, Fritsch retractor.

and the peritoneum. It allows for traction and dissection and eliminates undue direct pressure against either of these structures. Whenever speed is mandatory, this maneuver greatly reduces the dissection time. Occasionally, the bladder is freed from the underlying tissue without coming into contact with the peritoneal fold at all.

11. The bladder is again tucked under the lip of the retractor on the right (with the afore-mentioned fascia) and the retractor on the left is also put on traction (Fig. 7). The uterine segment is thus well exposed by using the retractors to facilitate the extension of the fascial incision.

12. A small transverse incision is made in the lower uterine segment wall (Fig. 8). This is extended bilaterally by finger traction until there is sufficient space for the extraction of the infant. The membranes are ruptured if intact, and the baby is delivered spontaneously, or with a special cesarean section forceps or vectis. Removal of the retractors from the wound often makes extraction of the child easier, especially in cases in which there has been previous surgery with formation of a heavy scar.

13. From this point on, the procedure resembles the usual cesarean section. After closure of the uterine incision, the bladder is returned to its usual position and need not be sutured to be held in place. No drains are required. The bladder may be distended by methylene blue solution for inspection of possible damage to its wall—but this is not routinely necessary.

14. The abdominal wound is closed in the usual manner with catgut sutures, but subcuticular No. 32 steel wire is employed in the skin. The rapidity of closure is facilitated by not having to suture the usual double layer of peritoneal tissue.

It has been traditional to leave an inlying catheter in the bladder connected to a Y tube for filling on occasion with sterile water or methylene blue, but this is not necessary. It is important that the bladder be empty, however. Therefore, an inlying catheter is placed in the bladder before surgery is begun.

The most important point in this technique is the utilization of the superficial fascia of the lower segment by a transverse incision. By making a small incision in this

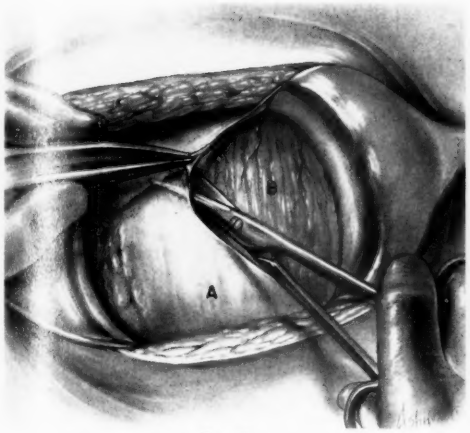

FIG. 7.

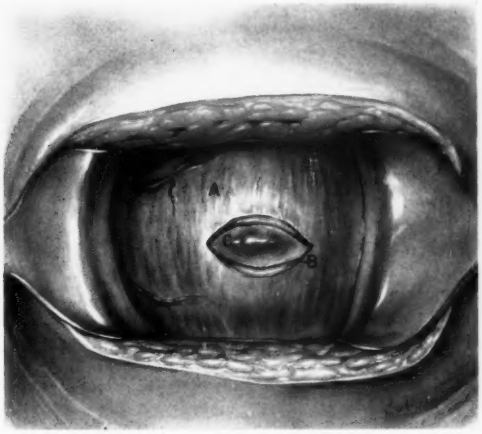

FIG. 8.

FIG. 7. *A*, Superficial uterine fascia. *B*, Lower uterine segment.
FIG. 8. Small transverse incision in the lower uterine segment wall. *A*, Lower uterine segment. *B*, The incision. *C*, Fetal membranes.

tissue and widening it, the following improvements are added: (1) less possible damage to blood vessels; (2) protection of the bladder and ureter; (3) protection of the peritoneal fold; (4) increased area for delivery of the child; (5) marked reduction in operating time and simplification of dissection; (6) increased adaptability of use to the low-lying, the scarred, and the obliterated peritoneal fold.

The extended dissection for exposure of the lower uterine segment is done in a tissue plane below the visceral peritoneum, as well as the bladder. The extension of the fascial dissection in order to attain this exposure is accomplished by: (1) blunt, wide dissection with the fingers; (2) sharp dissection by knife and scissors, only if there is considerable scarring from a previous cesarean section; (3) rapid spreading of the tissues by insertion of the retractor lip, followed by lateral traction—which is especially useful in situations in which the operator must move very quickly.

ANESTHESIA

Except when specifically contraindicated, spinal anesthesia has been the method of choice for cesarean section in this series. The maximum relaxation it affords facilitates the extraperitoneal dissection and provides more available space for removal of the child. Together with superior relaxation, it insures minimal depression of the child. This is most important, because very often the indication for the cesarean section is one in which the child is in jeopardy. (The fetal depression arising from most prolonged general anesthesias does not contribute to maintenance of the fetal ideal.) Furthermore, spinal anesthesia allows for maximal uterine tonicity with noticeable reduction of blood loss. Spinal block was used in all but 7 of these cases, and in no instance, did any postspinal complication arise to interfere with the postoperative course. Four of these 7 were done under general anesthesia, without obvious depression of the child. This fact is significant, in that there were no undue anesthetic effects upon the infant by prolonged time from skin incision to clamping of the fetal cord. Speed was of utmost importance in these cases, as well as in those cases of severe uterine hemorrhage. The same was true in the cases of prolapsed cord and in the 1 operation performed under no anesthesia, in which the patient was in a coma.

TABLE I.—RESULTS

Fetal		*Maternal*	
Mortality	5	Mortality	0
Hydrocephalic infant	2		
Placenta abruptio	2		
Hyaline membrane fetalis	1		
Morbidity	2	Morbidity	5
Hyaline membrane fetalis	1	Febrile, in coma at operation	1
Hydrocephalus	1	Urinary tract infection	3
		Mastitis	1

TABLE II.—POSTOPERATIVE OBSERVATIONS

	Successful (*105*)	*Elective peritoneal entry* (*11*)	*Failure* (*9*)
Ambulation within 24 hours	104	7	5
Catheterized after 24 hours	20	4	1
Inlying catheter	1	1	1
Febrile course	2	1	0
Regular diet and fluids, 8 hours	104	6	4
Repeated enemas in postoperative course	4	9	6
Postoperative distention; "gas pain"	2	10	5
Postoperative vomiting and ileus	0	1	1
Wound infection or drainage	0	0	0
Average number of injections for pain—100 milligrams demerol	3	6	5
Average postoperative day for dismissal	5	8	7
Patient reaction (improved postoperative comfort)	73	2	5

OPERATING TIME

Among the many criticisms of extraperitoneal cesarean section is one that it takes too long to do the operation. This not only includes the over-all time of the procedure from skin incision to skin closure, but also—and of even more importance—the time from skin incision to the clamping of the fetal cord upon removal of the baby. There are reports in which it has been recorded that 3 hours (average: 1½ to 2 hours) have been required for the procedure to be accomplished. Waters, however, reported an average time of 36 minutes for his technique. He is one of few to have done so. This is of great importance from the fetal standpoint, and of even greater concern to the mother, especially when general anesthesia is used. One may well visualize the added effect of a prolonged operation, together with the depressing action of prolonged anesthesia, on an already anoxic fetus and an already exhausted mother. It is easy to see how and why the valid criticism of prolonged time for the operative procedure came about.

The average length of time for the procedure in this series as recorded by the anesthesiologist is 40 minutes. The average length of time from skin incision to birth of the baby is 11 minutes. The longest procedure required 80 minutes, the shortest procedure, 18 minutes, the longest time to delivery of baby, 20 minutes, and the shortest time to delivery of baby, 4 minutes. These figures compare favorably with the averages given in performance of the standard transperitoneal operation. With experience, the dissection time can be readily reduced, and the use of the lower uterine segment fascia makes this possible. The fact that it is not necessary to suture the peritoneum for either peritonization or closure of the peritoneal cavity greatly reduces the time of wound closure.

RESULTS

There were 4 absolute failures: 2 with attempted extraperitoneal approach on the second section after a primary transperitoneal section; 1 on a third section after 2 transperitoneal sections; 1 on a fourth section after 3 previous extraperitoneal sections. In each case, there was such intense scarring that the dissection could not be carried out on either side of the bladder. In 2 of these, the bladder itself had been sutured to the lower segment by silk sutures. These cases were completed by transperitoneal section, but in each case, even this procedure was difficult.

INJURY TO PERITONEUM AND BLADDER; ENTERING THE PERITONEAL CAVITY PURPOSELY

No injuries to the bladder occurred in this series. There were 5 accidental injuries to the peritoneum: 4 small ones, sutured before the

uterine incision was made; and 1 large rent at the time of delivery of the child. For our purposes, these are considered failures as well as the ones in which the operation could not be accomplished at all. The peritoneum was entered purposely 11 times after the conclusion of the uterine closure; 6 times for tubal ligation; and 5 times for pelvic tumor. These latter were ovarian cysts. Total hysterectomy was accomplished twice for uterine myoma.

TABLE III.—REPEAT CESAREAN OPERATIONS PRIOR TO THIS EXTRAPERITONEAL SECTION

Previous operations	*No.*
1 transperitoneal section	53
2 transperitoneal sections	10
3 transperitoneal sections	2
4 transperitoneal sections	1
1 primary transperitoneal section, followed by 1 extraperitoneal section previously	3
1 extraperitoneal section	4
2 extraperitoneal sections	2
3 extraperitoneal sections	1

DISCUSSION

Feasibility of the use of the extraperitoneal approach to cesarean section when one plans to enter the peritoneal cavity after cesarean section is open to question. Tubal ligation at the time of section when the transperitoneal approach is used, neither adds to nor detracts from the postoperative end result. The peritoneal cavity has been already contaminated by the uterine effluvia and blood, no matter how carefully the operation has been done. The parietal and visceral peritoneum must be closed, leaving a possible attachment point for postoperative adhesions. Judging from the experience of reentry at a later date, the visceral peritonization is the greater offender. If the removal of the child, placenta, and accompanying blood spill is done extraperitoneally, none of this material enters the peritoneal cavity. The relatively innocuous and virtually bloodless tubal ligation technique such as the Pomeroy, done after the closure of the uterine incision following the extraperitoneal procedure with redraping and a change of gloves, produces much less of an insult to the peritoneal cavity. Furthermore, the closure of the parietal peritoneum, being the least offensive of the peritoneal closures, is in this instance the only one necessary. The same considerations hold true for any postcesarean section intraperitoneal exploration.

If the peritoneum is accidentally perforated in the course of the extraperitoneal dissection and this is recognized, it can be easily and rapidly closed before continuing the procedure. In such instance, the introduction of a small amount of air into the peritoneal cavity is the only result and this does not ordinarily cause postoperative difficulty. If, however, the peritoneum suffers wide damage, as can occur at the time of removal of the child from the uterus when there is insufficient space, the operation must be considered a failure from the standpoint of protecting the peritoneal cavity from contamination by the uterine contents. This contamination is not that of infection, as these are elective cases. Obviously, this is of even greater importance, if the uterine contents are presumed to be or are actually infected. In the latter instance, the entire principle of the procedure is negated.

The hazards, disadvantages, or complications of the extraperitoneal approach to cesarean section in the past have been as follows: (1) prolongation of operation time; (2) damage to the bladder and, less frequently, to the ureter; (3) damage to the peritoneum, especially in the presence of uterine infection; (4) instances in which the surgeon plans further intraperitoneal surgery; (5) severe hemorrhage due to injury of dilated vessels of the lateral uterine wall; (6) poor adaptation to situations in which immediate exploration of the pelvis is mandatory; (7) insufficient space for removal of the child.

The solution to the first 5 of these points is entirely dependent upon the care and skill of the operator and his familiarity with the technique. Mandatory exploration of the pelvis is primarily evident in the condition known as uteroplacental apoplexy or the Couvelaire uterus, at the time of severe or prolonged placenta abruptio. It is occasionally necessary to inspect the uterus to

determine whether it has been so badly damaged by the myometrial hemorrhage as to require its removal. In such situations, the value of the extraperitoneal approach becomes secondary to the problem at hand. The prevention of peritoneal insult, however, and the addition of so-called "gut shock" to an already precarious physiologic state in these cases often makes a great difference in the eventual recovery of the mother. Most certainly, the condition is uncommon, and fortunately, does not call for abdominal exploration very often. Quite frequently, the extent of uterine damage can be predicted from the appearance of the tissue in the area of the incision. The same may be true in rare situations of uncontrollable hemorrhage, undiagnosed ruptured uterus, or placenta previa.

Planned intra-abdominal surgery at the time of section appears superficially to be a contraindication to the elective extraperitoneal cesarean section. The findings postoperatively, however, bear out the observation that such intraperitoneal procedures as are done after the cesarean operation and after the uterine closure, entail less abdominal discomfort and complications than those done with the transperitoneal approach. It is not our purpose to discuss the routine performance of appendectomy at the time of the section or the hazards of postcesarean section myomectomy, for these are still highly controversial matters. A definite reduction of clinical postoperative abdominal symptoms is accomplished by using the elective extraperitoneal approach in those cases in which ordinarily an intraperitoneal postcesarean procedure is planned.

SUMMARY AND CONCLUSIONS

One hundred and twenty-five cases of elective extraperitoneal cesarean section have been presented. Of these, 4 were failures in that the procedure could not be carried out. In 5, there was accidental peritoneal entry, 4 of which were repaired immediately. There were 9 failures in 125, or 7 per cent. The peritoneal cavity was purposely entered 11 times: 6 for tubal ligation, and 5 for pelvic tumor. Spinal anesthesia was used in the majority of cases without complication. The technique of elective extraperitoneal cesarean section is a modification of the Norton dissection, and emphasis has been placed on the details of surgical technique and anatomy. The value of dissection in the fascial plane overlying the lower segment is emphasized. Reduction of time from onset of dissection to removal of the child, as well as over-all time for the procedure as an improvement over the traditional record, is discussed. Postoperative results and benefits are listed, and the absence of injury to the bladder is noted. The use of the procedure when subsequent pelvic surgery is indicated is suggested in view of improved results.

In conclusion, the excellent postoperative recovery and the minimal amount of postoperative discomfort are indicative of the value of the extraperitoneal approach to cesarean section as an elective procedure. This method is a distinct departure from the time-honored indications for its use. It is reasonable to expect that with this technique, anyone capable of a good standard transperitoneal operation can utilize the elective extraperitoneal for the majority of cesarean sections performed with a much improved postoperative course for patients and a minimum of trauma to vital organs. It does not add to postoperative complications and can be used in most elective situations when cesarean section is indicated. Its use for the cesarean portion of an extended operative endeavor, when subsequent invasion of the peritoneal cavity is indicated, considerably reduces peritoneal insult and enhances the postoperative course of these patients as well. There is no substitution for not entering the peritoneal cavity, insofar as postoperative comfort and recovery are concerned.

The prevention of distention, ileus, and postoperative adhesions with their attendant possibilities of pain and intestinal obstruction are obvious. The total avoid-

ance of spill of uterine discharges, fluid, and blood by the extraperitoneal route, even in the absence of infection, obviates the irritant effect of this material upon the peritoneal cavity. This method, then, provides the opportunity for a more normal recovery of any patient who must be subjected to cesarean section for the successful delivery of her child, particularly when extraperitoneal cesarean section is electively chosen for the termination of a pregnancy. The operation need not be limited to those obstetric cases grossly infected from neglect or long trial of labor, for infection is not the only indication for the extraperitoneal cesarean section.

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HYSTERECTOMY IN 861 SELECTED CASES

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THIS STUDY concerns 861 abdominal and vaginal hysterectomies performed on the independent gynecologic service of the Charity Hospital of Louisiana at New Orleans, since 1953, in which the "open cuff" technique was employed. This technique was described by Barr and re-emphasized by Burch and Lavely. These are consecutive cases, all indigent, and all cared for on the wards of the Charity Hospital.

The surgery and ward care of these patients was by second and third year residents under the supervision of the visiting staff. The minimum follow-up on any patient was 4 months and the maximum follow-up was 4 years. With the exception of cancer patients, most patients were discharged from the clinic after the 6 month examination and instructed to return at any time that symptoms warranted. All operative and immediate and late postoperative complications as well as any that have occurred in the period after discharge from the hospital have been evaluated and recorded. Frequently, several examiners checked individual patients and made comments concerning their pelvic status. When these findings did not agree, those suggesting complications were included in the survey.

Since this technique was first introduced in 1953 several changes have occurred. First, vaginal hysterectomy has replaced abdominal hysterectomy as the operation of choice, and more liberal indications are being used for the vaginal approach. Second, less incidental cancer is discovered at the time of operation. This fact is due to the revision of preoperative cancer screening work-up which since 1957 requires Papanicolaou smears and cervical and endometrial biopsy on every patient scheduled for elective surgery. Prior to that time only those patients with a suspicious history or lesion were subjected to all of these examinations. A more complete work-up as suggested by Finn and the use of the colposcope will probably still further increase our preoperative diagnosis of unsuspected cancer. Third, subtotal hysterectomy has not been performed in the past 4 years. Other investigators have expressed similar views of preference for total hysterectomy.

The significance of a temperature of 100.4 degrees F. has been questioned in classifying morbidity. The cases in the present group have been divided into three categories: mild, in which the maximum postoperative temperature was 100 degrees F.; moderate, a maximum postoperative temperature of 101 degrees F.; and severe, a maximum postoperative temperature of greater than 101 degrees F. The duration of this temperature elevation is not taken into consideration, only its occurrence. This modified standard for morbidity is more critical than that usually employed.

In similar series, morbidity reports average approximately 38 per cent. In the present series, the morbidity would be close to that percentage had the standard morbidity criteria been used.

There is less morbidity after vaginal hysterectomy than after total abdominal hysterectomy. In explanation, these are the pertinent facts: (1) there were half as many cuff complications in the group with vaginal hysterectomies; (2) 31 per cent of this group received blood as compared to 53 per cent of the patients with total abdominal hysterectomies; and (3) the more serious imme-

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diate postoperative complications occurred in the total abdominal hysterectomy group. Hospital stay in the vaginal group was 1 day shorter. An evaluation of the open cuff technique in cesarean section-hysterectomy has already been reported from this service.

PRESENTATION OF DATA

Three hundred and fifty-five patients had vaginal hysterectomies. The average age of the negro patient was 33.6 years, and that of the white patient was 41.8 years. Five hundred and six patients had total abdominal hysterectomies. The average age of the negro patient in this group was 38.3 years, and that of the white patient 40.2 years. The average stay for the patient with vaginal hysterectomy was 6.8 days as compared to 7.5 days for the patient with total abdominal hysterectomy. No patients were sent home before the fourth day.

According to the morbidity classification the percentages given in Table I were observed.

The significant complications of abscess, hematoma, hemorrhage, seroma, and fistula are shown in Table II.

Granulation tissue was found in 30 per cent of all patients on their first postoperative visit regardless of the type of hysterectomy. This approaches the incidence cited by Israel. Only 2.5 per cent of all the patients in the vaginal hysterectomy group required the use of silver nitrate cauterization more than twice. Three per cent of the total abdominal hysterectomy group required this therapy. This is a minor complication since silver nitrate cauterization satisfactorily eliminated the condition in almost all cases. In 4 instances it was necessary to use the electric needle to fulgurate the granulation tissue and complete the therapy.

Seventy-six of 355 (21.4 per cent) patients with vaginal hysterectomies and 89 of 506 (15.6 per cent) with abdominal hysterectomies had postoperative complications of significance. The genitourinary tract was the source of trouble in 83 per cent of the 76 cases in the vaginal group but in only 25 per cent of the 89 cases in the abdominal group. The abdominal wound itself was the focus of trouble in 55 per cent of 89 patients. The remaining group of postoperative complications consisted of respiratory infections (including atelectasis and pneumonia), peritonitis, postoperative hemorrhage, jaundice due to blood transfusion reaction, and other minor complications (furuncles, labial hematoma, stress incontinence, and cuff infection).

TABLE I.—MORBIDITY

	Vaginal hysterectomy		*Abdominal hysterectomy*	
	No. of patients	*Per cent*	*No. of patients*	*Per cent*
Mild (100° or less)	79	22.2	95	18.8
Moderate (100°–101°)	186	53.4	286	56.5
Severe* (101° or higher)	90	25.4	125	24.7

*This group accounted for most of the prolonged hospitalizations.

Hemorrhage was an alarming major postoperative complication requiring re-exploration in 5 patients. In 2 patients in the vaginal hysterectomy group exploratory operations were performed because of vaginal bleeding before leaving the operating rooms. One had a retroperitoneal hematoma, the other an actively bleeding retracted pedicle. Six patients had significant postoperative bleeding after abdominal hysterectomy. Three of these had bleeding from the vaginal cuff which was controlled by vaginal packing alone. The 3 remaining patients in this group were re-explored on the first, second, and sixth postoperative day. In each of these cases a pedicle from which the ligature had either slipped or cut through the vessels accounted for the hemorrhage.

Blood transfusions were used liberally when indicated in these patients. Before elective surgery, all patients on the service

TABLE II.—COMPLICATIONS

	Vaginal hysterectomy		*Abdominal hysterectomy*	
	No. of patients	*Per cent*	*No. of patients*	*Per cent*
Abscess	0	0	7	1.4
Hematoma	7	1.9	13	2.6
Hemorrhage	1	0.3	6	1.2
Seroma	1	0.3	4	0.8
Fistula	0	0	0	0
Total	9	2.5	30	6.0

must have a minimum hematocrit of 35. Thirty-seven per cent of all patients undergoing vaginal hysterectomy received whole blood transfusions at the time of operation (31 per cent receiving 500 c.c. or less). Fifty-three per cent of all patients undergoing abdominal hysterectomy received whole blood transfusions (34 per cent receiving 500 c.c. or less). Twenty-two patients received an excess of 1,500 cubic centimeters. Only 1 of these was in the vaginal hysterectomy group.

Sixty-five per cent of all patients in the vaginal group and 54.8 per cent of all patients in the abdominal group received urinary antiseptics or antibiotics. The routine use of antibiotics is not followed. However, if a number of infected cases are present on the ward, antibiotics are used prophylactically.

The following complications occurred at the time of operation. The urinary bladder was lacerated 3 times in both the vaginal and abdominal groups. This accident was recognized in each instance at the time of its occurrence and repaired. No urinary tract fistulas developed. At laparotomy the large bowel was lacerated once and repaired immediately. In 4 cases it was necessary to resect a portion of small intestine because of involvement in dense pelvic adhesions. No fistulas developed in these patients. The vaginal approach was abandoned for the abdominal route during operation in 3 cases.

In 355 vaginal hysterectomy cases the following additional surgical procedures were done: anterior repair in 182 cases, posterior repair in 27, anterior and posterior repair in 91, enterocele repair in 11, right salpingo-oophorectomy in 11, left salpingo-oophorectomy in 6, repair of urethral diverticula in 3, repair of urethral fistula in 3, and repair of umbilical hernia in 3 cases.

These additional procedures were done in 506 total abdominal hysterectomy cases: left salpingo-oophorectomy in 52, right salpingo-oophorectomy in 39, bilateral salpingo-oophorectomy in 320, appendectomy (elective) in 202, secondary closure in 18, Marshall-Marchetti procedure in 4, anterior and posterior repair in 1, vena caval ligation in 2, hypogastric artery ligation in 13, intra-arterial transfusion in 1, and small bowel resection with end-to-end anastomosis in 4 cases.

DISCUSSION

Twenty-five different residents operated on the patients in this series. No deaths occurred in the series. The open-cuff technique is simple and allows one to detect most postoperative complications before they can jeopardize the patient's life. In the total abdominal hysterectomies a soft rubber Y drain can be placed through the open vaginal cuff beneath the vesicouterine peritoneal reflection and over the angles of the cuff. This provides an accessible egress for bleeding, simple oozing, or profuse hemorrhage.

Our technique for vaginal hysterectomy is essentially the Heaney type modified by a continuous purse-string suture placed in the peritoneum for its closure and allowing the vaginal cuff to remain open. The cuff edge is then run with an over-and-over continuous suture for hemostatic purposes. Jewett (7) concluded that there was no significant change in vaginal length after vaginal hysterectomy. Though no actual measurements of the postoperative vagina were made, patient histories (particularly with our open-cuff technique) corroborate his conclusions. The posterior culdeplasty as described by McCall is used in those instances in which an enterocele is repaired. This technique definitely lengthens the vaginal vault. The purse-string closure of the peritoneum does cause "bunching" of tissue at the apex of the vaginal vault but it has caused no complaints from the patients. The purse-string closure of the peritoneum has prevented possible prolapse of the fallopian tubes and the more serious prolapse of other viscera. Other infrequently reported complications have not been encountered in this series. There have been no instances of prolapse of the vaginal vault. Many of the patients had

such anatomic findings as a deep cul-de-sac and separation of the posterior commissure of the levator muscles. Ring points out that this complication may occur late, but it has not occurred in the cases followed up for 4 years.

Granulation tissue is looked upon as a minor complication. The open cuff technique may tend to cause more granulation than would be encountered with a closed technique. This may be due to the necessity for an area to heal where two cut edges are not approximated with a suture. It was necessary for 23 patients to receive silver nitrate application or electrocautery treatment 3 or more times. These patients all eventually responded to treatment. One rectovaginal fistula occurred after the repair of an old third degree laceration. No genitourinary vaginal fistulas occurred despite the frequent occurrence of urinary tract infection postoperatively.

Along with fistulas, the hematomas, abscesses, and seromas presented an incidence of 3.14 per cent by the open-cuff technique, essentially that reported by Johnson from another service in this hospital[1]. The 7 abscesses of the vaginal cuff occurred in the abdominal hysterectomy group and were secondary to pelvic infection present at the time of operation. The vaginal cuff is not routinely inspected before the patient leaves the hospital. A cuff is inspected when there is suspicion of infection. The clue is usually a relatively stable temperature elevation of the moderate type for 48 hours that fluctuates but does not have the true "septic" elevations and depressions.

We agree with Taylor who believes that hemorrhage and the urinary tract complications continue to be the impediments to the smooth postoperative course of the hysterectomy patient. On this service there was 1 postoperative death due to blood transfusion reaction. This occurrence was a further indication that whole blood should be used with extreme caution and with the properly indicated conditions. This death occurred in a patient not included in this series because of the difference of cuff closure used in the operation. Malnutrition and acute and chronic infection are constant occurrences which are encountered in this hospital. Many of the abdominal hysterectomies have been emergency operations performed upon patients who had iron deficiency anemia secondary to infection, blood loss, or poor nutritional status. Iron is prescribed preoperatively in all elective cases, but hematocrit levels often remain unchanged because of poor nutrition or poor iron utilization. The suspicion of persistent bleeding and shock prompt a re-exploratory operation if the Potter needle tap is positive, if the blood pressure is falling, or if the pulse rate increases despite adequate blood replacement. The diagnosis and treatment of postoperative hemorrhage may present a perplexing problem at times as in the case recently described by Jewett (6). Ligation of the anterior branch of the hypogastric artery is performed without hesitation when bleeding is excessive during operation or when re-exploration is necessary.

Several authors mention the genitourinary tract as the system most often involved in posthysterectomy complications. This is understandable with possible trauma to the serosa, proximity to infection, and distortion caused by uterine tumors to bladder and ureters. Dissection often interferes with some of the nerve supply to the bladder often necessitating prolonged periods with an indwelling catheter. It is surprising that ward infections are not more prevalent with the rapid turnover of patients due to the bed shortage for indigent patients, visitors with upper respiratory infections, the poor conditions of patients who are emergency admissions, and the extreme shortage of ward personnel properly trained in sterile technique. Under these conditions, the simple removal and reinsertion of a catheter may introduce an infection.

Incidental carcinoma is found in almost any large unselected series of hysterectomy cases, and a total of 10 such cases was found in this series. Nine cases were among the total

[1]Johnson, however reported on the closed cuff technique.

abdominal group and 1 in the vaginal group, a carcinoma in situ of the cervix. Of the abdominal group, 6 were carcinoma in situ of the cervix, 1 leiomyosarcoma, 1 adenocarcinoma of the fallopian tube, 1 malignant ovarian tumor, and 1 adenocarcinoma of the endometrium. The suggestions of Finn and the use of the colposcope will probably decrease this occurrence. Despite all screening methods used preoperatively, there will occasionally occur unsuspected cases of cancer of the fallopian tube or cancer of the ovary.

The type of hysterectomy done varied with the preoperative diagnosis. Seventy-five per cent of all the vaginal hysterectomies were indicated because of pelvic relaxation. Eighty per cent of the abdominal hysterectomies were done because of pelvic inflammatory disease, tubo-ovarian abscess, uterine fibroids, or a combination of those three conditions. The remaining indications for operation comprised such diagnoses as benign ovarian tumors, postmenopausal bleeding, endometrial polyps, chronic metritis, cystic changes in the endometrium, marked persistent basal cell hyperplasia of the cervix with ectropion, adenomyosis, and, in 1 case, symptomatic retrodisplacement of the uterus. The high incidence of uterine prolapse and pelvic relaxations can be appreciated in the negro patient in the vaginal hysterectomy group for these patients had an average of 7.5 pregnancies and an average of 6.4 deliveries per individual. Many of these patients had precipitate vaginal deliveries at home with or without the attendance of even a midwife. Infection with all its attendant complications was the primary indication in those patients operated upon by the abdominal approach.

Many of the patients of this series are being followed up, and others now discharged may present themselves later for re-examination. This study has reinforced the belief that this operative technique employing the open-cuff closure after hysterectomy (abdominal or vaginal) is safe, imposes few serious postoperative complications, is satisfactory in practically all instances of emergency and elective hysterectomy, and offers advantages over the closed-cuff procedure.

SUMMARY

1. Eight hundred sixty one cases of abdominal and vaginal hysterectomies have been reviewed.

2. The indications for the procedures have been discussed.

3. Our classification of morbidity has been presented.

4. Vaginal cuff complications have been described.

5. Revival of the open-cuff technique for closure after hysterectomy has been stressed.

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ANTIGENICITY OF TENDON

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THE ANTIGENICITY of tendon has been of interest to us for two reasons. First, when these experiments were performed, we were anticipating an early trial of composite tissue homografts of the entire flexor mechanism in the restoration of severely damaged human flexor tendons within the digital sheath. Preparation of the finger for such a graft involves a complete sacrifice of all of the sheath, followed by placement of the homograft directly in contact with delicate joint membranes and neurovascular structures. Even though the collagenous portion of a tendon homograft can be shown to persist, irreparable damage to surrounding host tissues might occur if the graft was sufficiently antigenic to cause a local antibody-antigen reaction followed by tissue autolysis and fibrosis. If a tendon homograft contains antigenic substances identical or similar to epithelial tissues, such an autolyzing type of host tissue reaction would be likely. As a result, subsequent fibrosis would defeat the purpose of the graft, even though morphologic studies have revealed persistence of the collagen and a preservation of the tensile strength.

A second reason for investigating the antigenicity of tendon is that tendon is a relatively simple tissue composed of 3 of the most widely distributed elements in living organisms. These are fibrocytes, collagen, and ground substance. Homografts of more complex tissues, such as skin, kidney, and endocrine tissues, involve the transfer of all 3 of these substances to some degree, yet most of our knowledge pertaining to the rejection of homografted tissues has been gained from the study of epithelium and endothelium. It seems pertinent to the general problem of homograft rejection, therefore, to study simple tissues such as tendon in an attempt to find out if collagen, ground substance, or fibrocytes are concerned in the rejection of more complex tissue grafts. Moreover, tendon grafts can be modified by relatively simple laboratory procedures to produce a transplant of pure collagen or collagen plus ground substance without living cells. Thus, even though the clinical need for human tendon homografts is relatively small, a study of the antigenicity of tendons is of indirect value in that the results of such a study can be applied to the general problem of composite tissue rejection.

Collagen, the most widely distributed biologic protein, has been assumed to be nonantigenic, or of such low antigenicity that it is unimportant in the over-all problem of foreign tissue rejection. The assumption that collagen is freely interchangeable between genetically diverse organisms, however, has been challenged by recent experiments, reported by Watson, Rothbard, and Vanemee, which show that collagen in solution is both antigenic and species specific. Additional evidence that collagen in another physical state may not be freely transferable was introduced by Maurer, who was successful in producing titratable antibody levels in rabbits by immunizing them with gelatin. These 2 reports have recently reopened the question of whether the collagen molecule is universal or individually specific in the spatial arrangement of its amino acids.

We have attempted to answer some of the questions concerning mesenchymal tissue individuality by studying the biologic reactions to heterologous and homologous tendon transplants. The reactions to fresh

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grafts and to various laboratory alterations of dog tendons after transfer to other animals have been investigated. The "second set" skin rejection phenomenon and the search for collagen antibodies by complement fixation tests have been utilized as a measurement of antigenic activity in the various preparations which we tested. Both methods of evaluating antigenicity are relatively crude compared to highly technical immunochemical determinations, but are probably precise enough to measure antigenic activity of the magnitude that might affect clinical transfer of mesenchymal tissues.

METHODS

Two experiments were performed. In the first experiment, the tail tendons were removed from 20 adult C57 strain mice. Ten of the tendons were washed in cold saline to remove blood and adjacent tissue debris and were then transplanted into the anterior abdominal wall of 10 C3H strain mice. The tendons were inserted through a midline incision and were placed in a subcutaneous pocket overlying the anterior abdominal fascia. Five of the remaining 10 tendons were fixed in formalin for 48 hours prior to transplantation; the other 5 tendons were digested with 3 fresh applications of active trypsin. The tendons fixed in formalin did not contain living cells, and the tendons which had been digested with trypsin were converted into relatively pure collagen. These artificial tendon preparations were also transplanted beneath the anterior abdominal wall of C3H mice. By utilizing 3 different preparations, it was hypothesized that a comparison of the host response to the 3 different preparations might yield important information concerning the location and characteristics of the antigenic substance, if antigenicity could be demonstrated.

Three weeks after transfer of the tendon grafts, a full-thickness skin graft was removed from the back of all of the C57 strain mice which had donated a tail tendon. The skin grafts were used to challenge the same C3H mice that had received the tendon grafts. The skin grafts were approximately 1 square centimeter in size and did not include the panniculus carnosus muscle. The grafts were sutured into a 1 square centimeter defect which was created on the dorsum of the recipient mouse. Stent fixation was used to prevent motion of the graft, and an adhesive bandage was applied over the stent. Our hypothesis was that, if the tendon graft contained antigens which were identical to the antigens in skin or which produced antibodies cross reacting with the antigens in skin, the challenging skin grafts would be rejected in a typical "second set" rejection time. A control experiment which was designed to measure the first set and second set skin rejection times for C57 strain to C3H strain transplants was performed simultaneously. In this experiment, 10 C3H strain mice from the same laboratory stock as those used in the tendon grafting experiment received full-thickness skin grafts from 10 C57 strain mice from the same stock as the tendon donors. Five days after slough of the skin graft, the control mice were grafted again with skin from the same donor. Survival times for the 2 grafts were recorded as first set and second set rejection times for C57 strain donors and C3H strain recipients.

In a second group of experiments designed to evaluate the antigenicity of pure collagen by complement fixation tests, fresh whole tendons from an adult mongrel dog were transplanted into the subcutaneous space of 4 mature albino rabbits. An additional 6 tendons from the same donor dog were extracted with acetic acid and the collagen thus obtained was reconstituted with sodium hydroxide and stored for future use as an antigen. Four weeks later the rabbits were challenged by skin grafts taken from the dog which had donated the tendons. A control experiment was performed by establishing typical first and second set skin rejection times for dog-to-rabbit transfers as was done in the previous

experiment. When the rabbits were challenged with skin grafts, they were also bled from the marginal ear vein and the serum was examined by a complement fixation test.

Reconstituted collagen for use as the antigen in the complement fixation tests was prepared in the following manner: Fresh dog tendons were minced with scissors and washed 6 times in cold water. After standing overnight in cold saline, they were transferred to 400 cubic centimeters of 1:10,000 (*p*H 3.8) acetic acid. During the next 4 days the volume was brought up to 8,000 cubic centimeters, and more acetic acid was added so that the final concentration was 1:1,000. The extraction process was carried out in a 4 degree C. cold room with the aid of continuous mechanical stirring. Dog collagen is not nearly as soluble as the rat tail collagen which is commonly used in laboratory extractions, and so it was necessary to use a larger volume and a lower *p*H than usual to obtain satisfactory yields. The undissolved residue was discarded, and the slightly viscous acetic acid extractant was filtered through a fine porcelain filter. The filtrate was then brought up to *p*H 7.1 by the addition of 0.1 normal sodium hydroxide. Immediately after adjustment of the *p*H to 7.1, a fine white flocculation appeared. The flocculi were collected by continuous centrifugation. If some of the solution containing flocculi is dialyzed against salt and then transferred to a grid and examined in the electron microscope, typical banded fibers with a 640° Angström period can be demonstrated. After the reconstituted collagen had been collected by centrifugation, it was lyophylized and stored in serum bottles at 4 degrees C. The extraction, reconstitution, and subsequent storage were all performed at a temperature of 4 degrees C. to prevent contamination with common molds. Extraction of 6 medium sized tendons in 8 liters of 1:1,000 acetic acid for 2 days yielded between 350 and 500 milligrams of fluffy, white, reconstituted collagen.

The complement fixation tests were performed by using a sensitized sheep red cell system which was incubated for 1 hour with the reconstituted collagen and a 1:20 dilution of fresh guinea pig complement. The 1:20 dilution of complement was selected instead of the usual 1:30 dilution because of the tendency of lyophylization to weaken antigenic potency. In all of the tests, tubes were also set up which contained sensitized sheep cells plus complement, with and without collagen, to be certain that the collagen alone would not fix complement. Because no dog collagen antiserum was available at the time when the complement fixation tests were being performed, a block system was utilized in which a series of antigen dilutions ranging from 1:2 to 1:64 were matched against a series of serum dilutions ranging between 1:2 and 1:64. This number of tests should have covered all of the antibody-antigen reactions which might be specific within a narrow range of concentrations.

RESULTS

Transformation from a pink color and soft texture to a dark color and leathery texture was selected as the end point in the measurement of survival time of the skin grafts. This end point was sharp and relatively sudden in animals as genetically diverse as those selected for our experiments. This end point was found to be considerably more reliable than separation of the grafts, for separation could be influenced by activity of the mouse and the type of cage. The mice were kept in individual cages to prevent destruction of the grafts by a companion. None of the grafts became infected and all of them took initially.

The "first set" skin grafts in the C57 to C3H strain control group had an average survival time of 8 days. The shortest survival time was 7 days and the longest surviving graft remained viable for 9 days. The second set grafts were applied as soon as all of the inflammatory reaction from the first graft had disappeared and the wound was completely healed. The second set grafts

TABLE I.—SKIN REJECTION TIMES—CONTROL GROUP

No.	1st set skin, days survival	2nd set skin, days survival
DONOR: C_{57} STRAIN MOUSE — RECIPIENT: C_{3H} STRAIN MOUSE		
1	7	4
2	7	4
3	9	6
4	8	5
5	9	5
6	9	6
7	8	6
8	8	5
9	8	5
10	7	5
Av.*	8	5.1
DONOR: ADULT MONGREL DOG — RECIPIENT: ADULT ALBINO RABBIT		
1	7	5
2	7	4
3	7	5
4	8	5
5	8	5
6	7	5
Av.*	7.3	4.8

*The difference between these averages is statistically significant.

persisted for an average of 5 days. The longest surviving second set graft remained viable for 6 days. The longest surviving second set graft did not last as long as the shortest surviving first set graft, thus clearly defining a first set and second set rejection time for this experiment. Control experiments for the dog-to-rabbit skin transfers in the second group of experiments revealed a similar survival time for first and second set grafts (Table I).

The mice which had been immunized with fresh, trypsin-cleared and formalin-fixed tendon grafts retained their challenging skin grafts for 7 to 9 days—a typical first set rejection time. None of the skin grafts were rejected in less than 7 days.

Rabbits which were immunized by whole tendon grafts retained their challenging skin grafts for an average of 7 days. This was, again, a typical first set rejection time (Table II). Heterologous tendon grafts implanted in the subcutaneous tissue of mice and rabbits apparently do not contain antigens similar to, or in the same concentration as, those found in skin. Also, tendons apparently do not contain antigens which will stimulate the production of antibodies that cross react with the antigens in skin as measured by the skin rejection phenomenon.

None of the combinations of various dilutions of rabbit sera and reconstituted collagen fixed complement. Hemolysis was complete in all of the tubes. The transplantation of fresh dog tendons did not stimulate the 4 rabbits to produce dog collagen antibodies. As far as we could determine by complement fixation tests and skin graft rejection times, solid collagen is not significantly antigenic when introduced as a subcutaneous implant.

DISCUSSION

Previous attempts to demonstrate antigenicity of collagen by means other than skin rejection have been unsuccessful with two notable exceptions—those described by Battista and by Waksman. Maurer, using a quantitative precipitin test on human sera, was able to demonstrate antigenicity of gelatin; and Watson, Rothbard, and Vanemee reported that collagen in an acetic acid solution was antigenic for rabbits. The denatured state of the gelatin in Maurer's experiments probably prevents them from being applicable to the question of antigenicity in tendons, particularly since his experiments included an analysis of hydroxyproline to be certain that no impurities were carried over in the gelatin. A lack of tyrosine, the denatured state in which gelatin exists, and the low concentration of glycine, which prevents the molecule from attaining a rigid backbone structure, are the reasons usually given for previous failures to demonstrate antigenicity of gelatin. Maurer's experiments, however, strongly suggest that these assumptions may not be entirely correct. Watson, Rothbard, and Vanemee were successful in demonstrating antigenicity of rat collagen. In their experiments, rabbits were immunized with reconstituted collagen that had been redissolved in acetic acid and injected intraperitoneally in divided doses over a period of many weeks. After

a long term immunization by this method, they were able to demonstrate a rising titer of rat collagen antibody. Although Watson's group made an admirable effort to prove that the antibodies were directed against collagen alone, conclusive evidence of the specificity of collagen antibodies is difficult to obtain because of our incomplete knowledge of the structure and behavior of the collagen molecule. Reconstituted collagen, such as was used in Watson's and in our experiments, is relatively pure collagen, but unfortunately even minute amounts of an impurity such as tyrosine can produce antigenicity in an otherwise nonantigenic substance. Schmitt, Gross, and Highberger subjected a single 25 gram sample of collagen to 11 extractions with sodium chloride, 9 extractions with sodium phosphate (Na_2HPO_4), and 62 extractions with half saturated calcium hydroxide. Even after this, it was found that the final product still contained hexosamine in appreciable quantities. Schmitt and his associates did not speculate whether this small carbohydrate moiety is closely associated with or is an actual part of the collagen molecule. In their extraction experiments, tyrosine was always present in at least 0.41 per cent concentration. It is possible that the mucopolysaccharide latticework upon which the collagen fibrils develop may become incarcerated within the fibrils so that extraction by the usual chemical methods is impossible. Jackson has suggested that chondroitin sulfate may form stabilizing bonds between collagen chains, and adds that this may be the reason why pretreatment with hyaluronidase increases the solubility of native collagen in dilute acetic acid.

Fortunately, the basic problems encountered in the extraction and purification of collagen are not vital to the question of antigenicity of whole tendons. Since none of the fresh tendon grafts in our experiments were antigenic to a degree which could be measured by the rejection of challenging skin grafts or complement fixation tests, clinicians probably do not need to be concerned with antigenicity of the various substances found in normal tendon. Although collagen in solution may or may not be antigenic, depending upon the interpretation of Watson's data, solid collagen, with or without ground substance in the amounts present in fresh tendon, is not antigenic as we have evaluated it.

TABLE II.—SKIN REJECTION TIMES—TENDON TRANSPLANT GROUP

No.	Initial graft	Challenging skin graft, days survival
	DONOR: C_{57} STRAIN MOUSE — RECIPIENT: C_{3H} STRAIN MOUSE	
1	Fresh tendon	8
2	Fresh tendon	8
3	Fresh tendon	7
4	Fresh tendon	8
5	Fresh tendon	7
6	Fresh tendon	7
7	Fresh tendon	9
8	Fresh tendon	9
9	Fresh tendon	7
10	Fresh tendon	9
11	Formalin fixed tendon	8
12	Formalin fixed tendon	9
13	Formalin fixed tendon	7
14	Formalin fixed tendon	8
15	Formalin fixed tendon	8
16	Trypsin cleared tendon	9
17	Trypsin cleared tendon	9
18	Trypsin cleared tendon	7
19	Trypsin cleared tendon	7
20	Trypsin cleared tendon	8
	Average*	7.9
	DONOR: ADULT MONGREL DOG — RECIPIENT: ADULT ALBINO RABBIT	
1	Fresh tendon	8
2	Fresh tendon	8
3	Fresh tendon	7
4	Fresh tendon	9
	Average*	8.0

*The difference between these averages and the averages of the first set graphs in Table 1 is *not* statistically significant.

Failure of the transferred fibrocytes to be significantly antigenic is not as easily dismissed as the failure of purified collagen to be antigenic. Although specific data on fibrocytes in pure culture are not available, there is strongly suggestive evidence, as reported by Billingham and associates, that the tissue specificity antigens are complex amino acid-polysaccharide combinations which are found on all nucleated cells. Billingham (2) has suggested that the most likely explanation for our results was that the small dose of antigen delivered by a

relatively acellular tissue such as tendon was not sufficient to evoke a subsequent accelerated tissue rejection. This hypothesis could have been investigated further by dissecting out a few more milligrams of collagen from the donor mouse and implanting it with the tail tendons, but since the tail tendon represents a relatively tremendous graft in terms of human restorative problems, we did not pursue the question of dosage any further. We agree that the relatively small dose of antigen probably accounts for the first set skin rejection results, but we also raise the question of whether a mechanical factor might also be involved. The experiments presented in the preceding article revealed some variation in the survival time of fibrocytes in transplanted tendons. Since the survival time of the fibroblasts correlates somewhat with the age and physical density of the tendon, could not a millipore filter effect be exerted by the densely packed collagen bundles in some instances? Such an effect conceivably could prevent some of the fibroblasts from being contacted by circulating antibodies. A similar hypothesis appears tenable in cartilage grafts where it has been shown that the chondrocytes persist indefinitely. A limited application of the same hypothesis might apply to tendon or small portions of a tendon as well.

In conclusion, it should be emphasized that the "second set" skin rejection phenomenon and complement fixation tests using reconstituted collagen as an antigen are relatively gross determinations of an extremely sensitive and highly specific biologic phenomenon. Flocculation tests or a study of mesenchymal tissues transplanted into animals with a high titer of circulating antibodies after immunization by Watson's technique would be more sensitive indicators of the antigenicity of the substances which are transferred in whole tendons. The surgeon who desires to transfer homologous tendon, however, is probably not embarrassed by any antigenic properties of this magnitude and in all probability does not lose complex tissue grafts such as skin or kidney because of antigenic properties of the mesenchymal components of these tissues.

SUMMARY

In order to measure the antigenicity of homologous composite tendon grafts, which are currently being evaluated in the restoration of selected flexor tendon injuries, and to investigate the antigenicity of some of the mesenchymal components of other complex tissue grafts, mice and rabbits were immunized with various types of tendon transplants. The animals were subsequently challenged with skin grafts from the original donors. In other experiments, the sera from recipient animals were subjected to complement fixation tests using reconstituted collagen as an antigen. Using these tests, we were not able to demonstrate clinically significant antigens in whole tendons or any of their components. It appears now that solid collagen or fresh tendons can be heterologously or homologously transplanted without significant immunologic reactions. The possible explanation and implications of these results are discussed.

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A NEW METHOD FOR ESTABLISHING A GASTROSTOMY OR JEJUNOSTOMY WITH EVALUATION IN 26 PATIENTS

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PATIENTS with unresectable obstructing lesions of the esophagus or stomach may require a gastrostomy or jejunostomy for feeding purposes. Many methods of forming gastrostomies and jejunostomies have been described but none appears to be entirely satisfactory.

A suitable gastric or jejunal stoma should: (1) be readily constructed; (2) be easily cared for by the patient or his family; (3) not leak; (4) not lead readily to infection in the peritoneal cavity or abdominal wall.

In 1956 a method of creating a gastrostomy or jejunostomy by using a prosthesis was reported with a description of its use in 3 patients (1). The longest follow-up period was 4 months. The operation described was considered to be superior to existing means of creating a gastrostomy or a jejunostomy. Since the original report, this method has been used in an additional 23 patients, some of whom have been followed up for periods up to 18 months. The present report is an evaluation of the procedure based on these 26 cases.

RESULTS

Data concerning the 26 patients in whom the prosthesis has been used follow: There were 24 gastrostomies and 2 jejunostomies. Twenty of the patients were operated upon at The New York Hospital, 8 by attending surgeons and 12 by residents. In the remaining 6 patients, the procedure was done elsewhere by attending surgeons in 4 cases and by residents in 2. The operations were accomplished without difficulty by these surgeons who were acquainted with the method only through its description in a previous publication (1).

There were 19 males and 7 females ranging from 30 to 86 years of age with an average age of 64.9 years: 2 males were in the fifth decade of life, 4 in the sixth, 5 in the seventh, 7 in the eighth, and 1 in the ninth; 1 female was in the fourth decade, 1 in the sixth, 2 in the seventh, 3 in the eighth. The patients were followed up for from less than 1 week to as long as 1½ years postoperatively. Sixteen were observed for periods longer than 2 months: 6 for 2 to 4 months, 1 for 4 to 6 months, 6 for 6 to 9 months, 1 for 9 to 12 months, and 2 for 16 to 18 months.

Postoperative deaths. Five patients died while in the hospital.

CASE 10. A 62 year old man had had x-ray therapy for carcinoma of the middle and lower thirds of the esophagus. After a short period of relief of symptoms, progressive dysphagia developed. On April 18, 1957, using a nylon prosthesis a gastrostomy was established under local anesthesia. Tube feedings begun the next day were well tolerated. His general condition began to improve, but suddenly on the fourth postoperative day massive hematemesis occurred and he expired. Postmortem examination revealed that the esophageal tumor had perforated into the right pulmonary artery and lung. The prosthesis had not leaked and skin around it was in excellent condition.

CASE 25. A 76 year old male had carcinoma of the proximal third of the stomach with extension to the distal esophagus causing complete obstruction. At exploratory laparotomy, multiple peritoneal and hepatic metastases were noted. On June 23, 1958, a gastrostomy using a nylon prosthesis was performed under general anesthesia. He tolerated the procedure well, and gastrostomy feedings were started on the third postoperative day. However, he deteriorated progressively and died 9 days after operation. Autopsy was not performed. At the time of death the abdominal wound was healing well, the gastrostomy had not leaked, and the skin about the prosthesis was not excoriated or inflamed.

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CASE 16. A 69 year old male had an inoperable carcinoma of the middle third of the esophagus. On September 23, 1957, a gastrostomy using a nylon prosthesis was established under general anesthesia. Postoperatively, he developed paralytic ileus which progressed despite aspiration of the stomach through the gastrostomy prosthesis. On the fifth postoperative day, he eviscerated and the wound was closed immediately under local anesthesia. Despite all supportive measures he died the following day. Postmortem examination revealed pulmonary edema, hyperemia, and emphysema. There was no free fluid in the peritoneal cavity. The gastrostomy site was intact and the skin about the prosthesis was completely unremarkable.

CASE 18. A 69 year old male had obstruction of the esophagus due to carcinoma metastatic to the neck. On January 30, 1958 under local anesthesia, a gastrostomy was performed using a nylon prosthesis. He tolerated the procedure well but on the night of operation he expired suddenly, the terminal events being consistent with a pulmonary embolus. Autopsy was not performed.

CASE 11. A 75 year old white male underwent an exploratory operation on April 18, 1957 with the finding of a carcinoma of the distal third of the esophagus extending to the stomach and liver. Because of fixation and the large size of the tumor, the stomach could not be brought up readily to the abdominal wall, and gastrostomy was performed with difficulty. A wound infection developed on the second postoperative day and the wound was drained. This infection spread to involve the site of the gastrostomy. Nevertheless the patient was able to take feedings through the gastrostomy beginning on the fifth postoperative day. The prosthesis became loose and sloughed out on the eighteenth postoperative day. A gastrocutaneous fistula persisted, however, through which tube feedings were continued. The patient's course was slowly but steadily downhill and he expired on May 18, 1957, one month after operation.

Nonfatal complication. There was 1 nonfatal complication.

CASE 4. A 57 year old woman had a wound infection that led to extensive maceration of the skin about the prosthesis. On May 29, 1958 this patient with carcinoma of the thoracic esophagus extending into the trachea at the level of the bifurcation underwent an exploratory thoracotomy, laparotomy, and gastrostomy using a nylon prosthesis. She had a thick abdominal wall and, because the central core of the prosthesis was short, it was brought out through the lower end of the main wound rather than through the customary separate stab wound. Despite this procedure the central core still did not protrude beyond the skin and the cap could not be applied. Hence an extension was made immediately and attached to the main stem while the patient was in the recovery room. The wound appeared unremarkable for the next few days. On the eighth postoperative day acute cholecystitis developed and she underwent emergency cholecystostomy. Shortly afterward a wound infection was noted in the lower angle of the original laparotomy incision near the central core of the prosthesis. Subsequently leakage developed about the gastrostomy and also about the cholecystostomy tube. This led to moderately severe maceration of the skin in these regions. A rubber feeding tube was inserted into the jejunum through the gastrostomy prosthesis and the patient's nutritional status was maintained. By utilizing meticulous local care, the effects of leakage from the cholecystostomy and gastrostomy were controlled. After excoriation of the abdominal wall had healed the patient received x-ray therapy and was discharged to continue gastrostomy feedings at home. At the time of discharge, the skin of the abdominal wall was healed, the gastrostomy was functioning well, and her general condition was improved. She died at home 8 months after the gastrostomy had been established.

The remaining 20 patients (18 with gastrostomy and 2 with jejunostomy) were followed for periods of from 2 weeks to 1½ years. Although some have been able to take a limited amount of fluids by mouth, the majority have taken all of their nourishment via the prosthesis. There has been no leakage and the skin about the prosthesis has not become macerated.

In 2 instances, following x-ray treatment in one and retrograde bougienage in the other, the patients improved to the degree that the gastrostomy was no longer needed. In each case, the prosthesis was removed without incident at a second operation, after 18 months and 6½ months.

The prosthesis was removed by an elliptic incision of the skin and layers of the abdominal wall down to and including the stomach in the patient who had had prosthesis for 18 months. The tract about the central core was lined by firm granulation tissue. There was slight atrophy of mucosa in the area immediately adjacent to the inner flange but the stomach was otherwise unremarkable.

DISCUSSION

With the exception of 1 patient, in whom marked paralytic ileus and evisceration de-

veloped, the gastrostomy did not contribute to the demise of any patient. Complications arose in 2 instances only. In both cases, wound infection developed that led to leakage about the prosthesis in one patient and eventual slough of the prosthesis in one.

The fatal complication rate was 1 in 26 (3.8 per cent) while the rate of nonfatal complications was 2 in 26 (7.7 per cent).

Connar and Sealy reviewed 125 gastrostomies done between 1944 and 1954 and reported a fatal complication rate of 5.6 per cent and a nonfatal complication rate of 14.4 per cent. Gibbon and associates described a modification of Glassman's method and their results in 18 patients. In 2 cases the gastrostomy was not opened. Two of the remaining 16 had slight to marked leakage with skin irritation, a nonfatal complication rate of 12.5 per cent.

Other series reported on this subject by Sweet, Cooper and Buxton, Lyall and Leider, and Clay had fatal complication rates of from 9.8 to 34.8 per cent and nonfatal complication rates of from 12.1 to 61.9 per cent.

A review of 54 gastrostomies performed at the New York Hospital prior to 1956 revealed a nonfatal complication rate of 37 per cent.

In comparison with the use of the prosthesis as described, there is a lower incidence of both fatal (3.8 per cent) and nonfatal complications (7.7 per cent).

Many of the patients gained weight initially after the creation of the gastrostomy. However, as their underlying disease progressed, they usually manifested a gradual loss of weight and a downhill course culminating in death.

The fact that different surgeons with varying amounts of training and experience performed this operation with low morbidity and mortality rates emphasizes the ease with which the gastrostomy can be done. Almost all of these patients were able to feed themselves through the gastrostomy with a minimum of instruction, attesting to the simplicity of the prosthesis and the little care needed for its maintenance and use. The absence of infection and skin irritation for as long as 1½ years postoperatively indicates that the prosthesis is well tolerated and that it does not leak.

When changes in thickness of the abdominal wall occur, the outer flange can be turned down or loosened, depending on whether there has been loss or gain of weight. If a patient gains weight and the abdominal wall gets thicker, unscrewing the outer flange a few turns will prevent undue pressure against the skin surface and thus prevent skin irritation. An occasional individual may have excessive granulation tissue around the central core at its point of emergence through the skin of the abdominal wall which may require occasional cauterization with silver nitrate. In most instances, however, this does not occur and dressings about the prosthesis are unnecessary.

The need for gastrostomy still exists for many patients with obstructing, unresectable lesions of the esophagus or upper portion of the stomach with esophageal involvement. Providing nourishment during periods of x-ray irradiation therapy is one important reason for this procedure. Even in those patients in whom no further treatment is possible, alimentation through the prosthesis has been comforting and palliative. Any fluid and full meals that have been prepared in an electric blender may be given without distress. After gastrostomy or jejunostomy, feedings may be begun as soon as desired unless there is some contraindication. By the end of 2 weeks, most of these individuals are able to take from 400 to 500 cubic centimeters of nourishment at any one time without distress. The operation described has proved to be simple, safe, and satisfactory and provides a method of feeding generally unaccompanied by leakage, infection, discomfort, or skin irritation.

Experimental studies are being pursued in attempts to simplify the prosthesis and develop types that are suitable for temporary use. These should be able to be removed without requiring a second operation.

It was originally planned that the large inner flange drawn up against the gastric wall by screwing down the outer flange would prevent gastric contents from escaping along the fistulous tract. While this may be of value in the early postoperative period, of perhaps equal or greater importance later on may be the baffle-like effect produced by the threads along the central core. In 1 patient from whom the prosthesis was removed at operation, fibrous tissue was noted to have grown between the threads forming a mold of the central core. While the core could be rotated freely, it could not be moved readily up or down in the tract, even without the obstruction produced by the inner and outer flanges.

Hence it is possible that the flanges can be eliminated without incurring leakage. This would simplify removal of the prosthesis since it could be unscrewed from the abdominal wall.

Should it be found that the inner flange is essential to prevent leakage a detachable or flexible flange may still allow the prosthesis to be removed without operation.

SUMMARY AND CONCLUSIONS

A new method using a prosthetic device for the formation of gastrostomy or jejunostomy has been used in 26 patients.

There were 5 deaths in the immediate postoperative period only 1 of which could be causally related to the performance of the gastrostomy—mortality rate of 3.8 per cent. Wound infection occurred in 2 patients—complication rate of 7.7 per cent.

The operation was successfully performed by a variety of surgeons, many of whom were acquainted with the method only through its description in a previous publication.

With this technique a gastrostomy or jejunostomy is readily constructed. It is easily cared for by the patient or his family, does not leak, and does not lead readily to infection in the peritoneal cavity or in the abdominal wall.

Modifications of the prosthesis are being tested in an attempt to eliminate the need for operative removal.

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PERSISTENT DESCENDING MESOCOLON

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IN CONTRAST to positional anomalies of the right half of the colon, which are not uncommon, similar anomalies involving the left half of the colon are rarely seen. To be reported herein are 3 examples of a rather clear-cut positional anomaly of the descending colon. This anomaly may give rise to clinical symptoms and may simulate internal hernia both clinically and roentgenographically. This anomaly has been characterized by the term "persistent descending mesocolon."

The condition is characterized by abnormal persistence of the descending mesocolon from a point beginning at or just below the splenic flexure to the sigmoid colon. There is thus created an actual or potential recess behind the abnormal mesocolon in which all or part of the small bowel may be contained. The anomaly is no doubt more common than would appear from a survey of the literature, in which only a very small number of cases of clinical significance have been reported.

EMBRYOLOGY

So complex a process is the embryonic rotation and fixation of the intestine that it is surprising that more anomalies do not occur. It is not difficult to become lost in describing the gyrations of the midgut as it leaves and re-enters the embryonal coelomic cavity between the fifth and tenth weeks of gestation. During the fifth week the elongating intestinal tube herniates outside of the primitive coelom and continues to develop in length. Before it returns it undergoes a 180 degree rotation counterclockwise about the omphalomesenteric vessels. Reduction of the midgut loop into the abdomen occurs rather abruptly during the course of the tenth week.

As the coils of small bowel re-enter the abdomen, they do so first on the left. The hindgut is pushed to the left by the re-entering small bowel, thus delineating the future descending colon. On re-entering, the terminal ileum and cecum initially lie in the subpyloric area. As elongation of the colon continues, the cecum and ascending colon rotate an additional 90 degrees eventually ending up in the right lower quadrant. This rotation is generally complete by the twelfth week of fetal life.

Up until the fourth month of gestation, there is no fixation or fusion of the various mesenteries (Fig. 1A, C). The bowel retains a potential, though somewhat restricted, mobility by virtue of this lack of mesenteric attachment. After the fourth month, how-

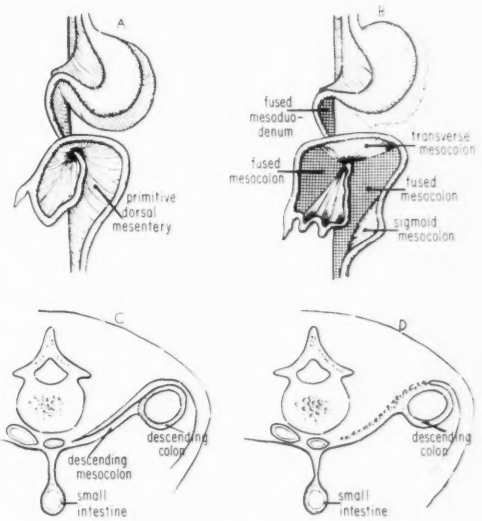

FIG. 1. A, C, Condition at end of fourth month of gestation, showing primitive dorsal mesentery. B, D, Sites of fusion of primitive dorsal mesentery. Adapted from Arey (1).

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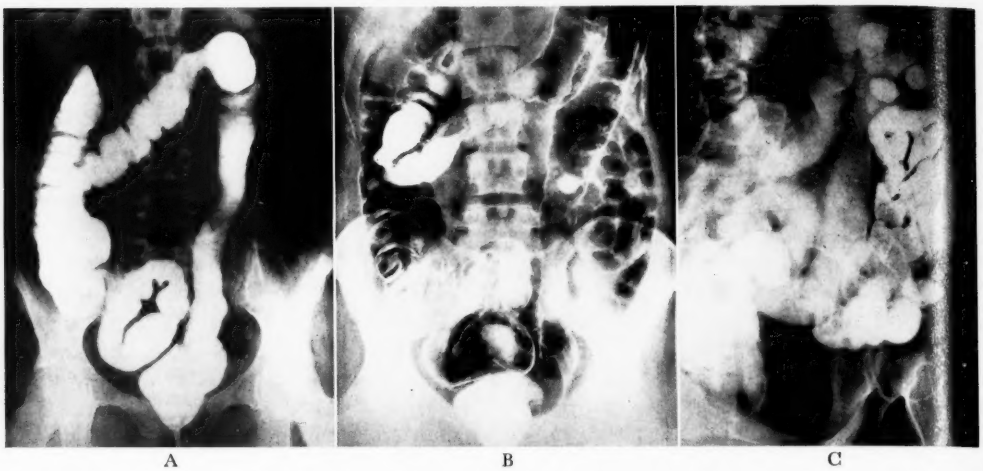


A B C

FIG. 2. Patient N. G. A, Displaced descending colon. B, Loops of small bowel trapped to left of descending colon. C, Detail of small bowel loops in left iliac fossa.

ever, this condition is altered as secondary fusions begin to fix various portions of the intestine into permanent position. Thus by the end of the fifth month the mesenteries of the ascending and descending colon have become fused against the dorsal body wall, the fusion proceeding mediolaterally (Fig. 1B, D). The final line of fusion laterally with the parietal peritoneum is well demarcated, the fascial fusion layer of Toldt. The transverse mesocolon remains free to a large extent, although it does fuse with and cover the duodenum as it crosses it. Similarly, the mesosigmoid remains largely free, but the mesorectum is obliterated as the rectum assumes its position against the sacrum. This obliteration of large portions of the primitive dorsal portion of the mesentery by secondary fusion and the resulting fixation of the gut is characteristic of the anthropoid apes and man. It does not occur in the quadrupeds and has therefore been related to the upright posture.

CASE REPORTS

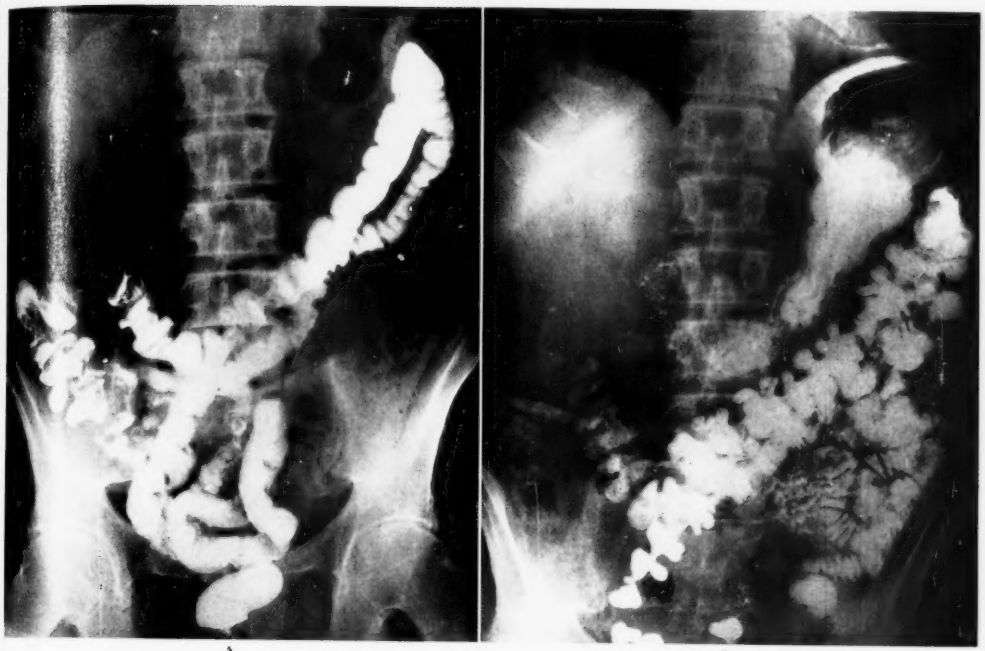
CASE 1. N. G., a 33 year old white female, complained chiefly of constipation of 10 to 12 years' duration which was becoming more marked recently. In addition, she complained of recurrent episodes of cramping paraumbilical pain, which were not associated with nausea or vomiting. The attacks of cramping abdominal pain were occasionally quite severe.

Roentgenographic examination of the colon after one of these attacks (Fig. 2) revealed the descending colon in a position rather far medially along the left border of the spine. Lateral to the descending colon was a group of air-filled small bowel loops. To the roentgenologist this was very suggestive of an internal parasigmoidal hernia through a pathologic opening in the mesocolon.

After another attack, a simple roentgenogram of the abdomen and "partial" contrast enema again revealed gas-filled loops of small bowel lateral to the descending colon. Again, the roentgenologist interpreted the films as representing an internal hernia, with the small bowel loops "so arranged that one might strongly suspect that they are contained within a peritoneal pouch."

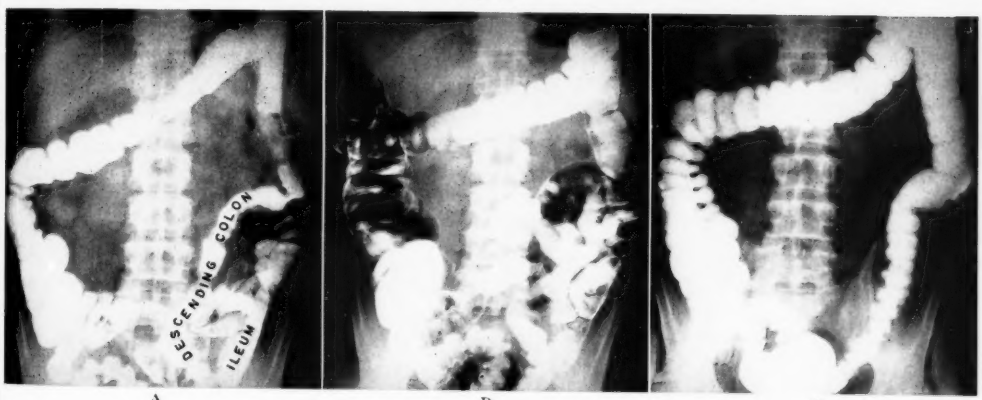
CASE 2. F. S., a 69 year old white male, was seen during an attack of severe cramping pain in the lower abdomen associated with nausea and vomiting. The attack was severe enough to necessitate hospitalization. Because the patient was known to have cardiac disease, with hypertensive and coronary disease, it was suspected that he might have had a mesenteric vascular occlusion. However, his course did not corroborate this diagnosis and the attack subsided rapidly.

After the attack, a barium enema (Fig. 3) revealed the descending colon to be in an abnormal position near the midline, with gas-filled small intestinal loops demonstrated on all films far lateral to the descending segment of colon. Again, the roentgenologist interpreted the films as representative of an internal hernia, possibly through the mesosigmoid (intersigmoid hernia).



A B

FIG. 3.



A B C

FIG. 4.

FIG. 3. Patient F. S. A, Displaced descending colon. B, Ileal loops in left iliac fossa showing characteristic straight left border.

FIG. 4. Patient L. B. A, Displaced colon. B, Ileal loops in left iliac fossa. C, Postoperative roentgenogram showing descending colon reposited in left iliac fossa.

CASE 3. L. B., a 49 year old male, complained of recurrent episodes of crampy abdominal pain, chiefly in the left lower quadrant. These attacks were occasionally severe enough to incapacitate the patient. He would at times obtain relief by lying on his right side. Occasionally the attacks were accompanied by nausea and vomiting, as well as a "drawing" sensation toward the left scrotum.

On roentgenographic examination of the colon (Fig. 4), the descending colon was far medial to the normal position. Lateral to the descending colon a number of ileal loops were coiled in the left lateral

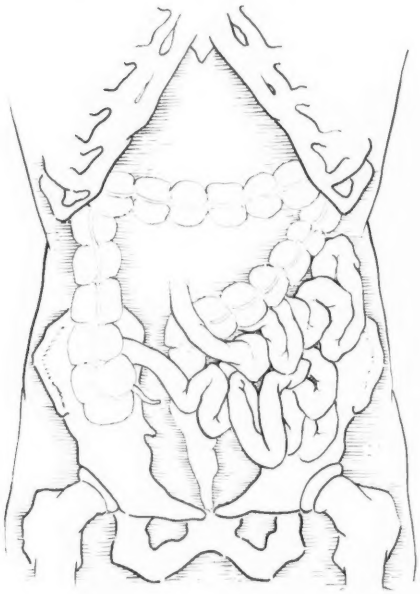


FIG. 5. Diagrammatic representation of findings at operation in Case 3.

gutter and left iliac fossa. The roentgenologic diagnosis was possible internal parasigmoidal hernia through a defect in the mesocolon.

Because of the recurrent attacks of incapacitating abdominal pain and the abnormal roentgenologic findings, the patient was subjected to exploratory laparotomy. At operation the immediate striking finding was the absence of small bowel from its normal position in the abdomen. The distal two-thirds of the descending colon swung free as an unfused mesocolon. Created thus was a paracolic fossa on the left, into which recess the entire small bowel from proximal jejunum to terminal ileum was crowded (Fig. 5). This recess was bounded superiorly by the fusion of the abnormal mesocolon with the posterior parietal peritoneum, posteriorly by the parietal peritoneum of the left colic gutter and the iliac fossa, anteriorly by the "persistent descending mesocolon," and inferiorly by the pelvic brim. At one point the terminal ileal mesentery was fused to the sigmoid mesocolon, a factor which was instrumental in preventing reduction of the small intestinal loops into the main abdominal cavity.

The small bowel was replaced in its normal position. The parietal peritoneum in the left gutter was incised along its whole length. The abnormal fossa was obliterated by suturing the descending colon to the lateral cut edge of parietal peritoneum. Thus, an approximation of the normal line of fusion was obtained.

The postoperative course was not remarkable. Since the operation the attacks of crampy abdominal pain have disappeared. A postoperative barium enema (Fig. 4C) revealed the descending colon in a relatively normal position. The small intestinal loops previously visualized lateral to the descending colon were no longer seen, save for 1 small slightly gas-filled loop. The anomaly appeared roentgenographically to have been corrected.

DISCUSSION

Congenital, positional anomalies of the colon may be roughly divided into two main groups: (1) anomalies of rotation and (2) anomalies of fixation. Among the anomalies of rotation, to mention 2 examples, are the left-sided ascending colon and highlying cecum. Among the anomalies of fixation are persistent ascending and descending mesocolon. On the right, the extensive mobility of the right half of the colon, caused by a persistent mesocolon, may result in volvulus of the cecum or ascending colon. On either side, lack of fusion may result in a right (Waldeyer's) or left (Landzert's) paraduodenal hernia.

The anomaly of interest herein is lack of fixation of the descending colon. Three types which have been reported are illustrated in Figure 6. In Figure 6A, both the right and left half of the colon have failed to be fixed posteriorly. There is no transverse colon. In Figure 6B, three examples of which are being reported herein, the descending colon swings on its mesentery to the midline or slightly to the left of the midline. In Figure 6C reported by Black and by Hamdy and Sorbur the descending colon swings even more acutely to the right and is fixed to the region of the cecum or even behind it.

When the descending colon possesses a mesentery as described in the operative case reported, all or part of the small bowel may be trapped behind it. This results in a rather characteristic roentgenogram (Figs. 2, 3, and 4).

Visualized after a barium enema (by reflux or air shadow), the loops of small bowel are seen lateral to the descending colon. In the left iliac fossa where they are

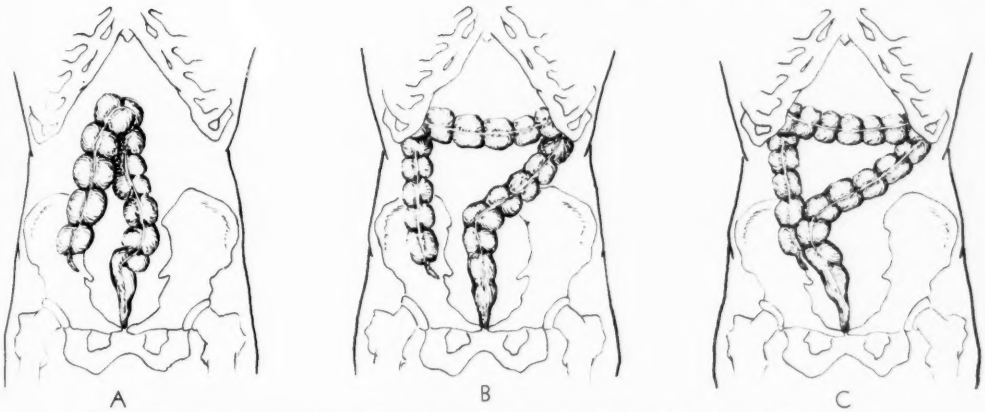


FIG. 6. The three types of descending colon displacement that have been described. A, Absence of transverse colon. B, Moderate displacement of descending colon to left. C, Marked displacement of descending colon with paracecal fixation.

crowded against the iliac bone, the loops form a characteristic straight line on the lateral margin (Figs. 2C, 3B, 4B). Roentgenologically the picture presented may be confused with that of the very rare intersigmoid hernia.

In a sense, this malformation is similar to the left paraduodenal hernia, both anomalies resulting from lack of fixation of the descending mesocolon. Left paraduodenal hernia has its embryologic origin when the reducing small bowel is caught behind the mesentery of the descending colon and is eventually incarcerated there by the fixation of the left half of the colon to the posterior wall. The sac, therefore, lies to the left of the duodenum. The inferior mesenteric vessels course in the fold which constitutes the anterior free margin of the sac. The small bowel passes beneath the root of the mesentery to be trapped behind the descending colon.

In the cases herein reported, the embryonic reduction of the small bowel is normal. The small bowel passes over the root of the mesentery to be imprisoned behind the persistent descending mesocolon. In this anomaly there is, of course, no sac nor can it be called a true internal hernia.

The clinical picture associated with this anomaly must be extremely variable. In all 3 of the cases reported here, the patients had episodes of crampy abdominal pain of greater or lesser severity. In Case 3, the symptoms were relieved preoperatively when the patient lay on his right side. Postoperatively, the episodes of cramps have disappeared. The mechanism of the pain is probably transient, incomplete obstruction occurring in the loops trapped behind the colon.

It should not be inferred from this report that corrective surgery is advisable if this anomaly is demonstrated on a roentgenogram. Severe recurrent symptoms of crampy abdominal pains, however, in conjunction with such a roentgenologic diagnosis should make one consider the advisability of corrective surgery.

Correction of the anomaly consists of simply replacing the small bowel in its normal position and fixing the descending colon in the left gutter. In the operative case reported this was done by incision of the parietal peritoneum laterally and suture of the descending colon to the peritoneal edge, thus simulating the normal line of fusion.

SUMMARY

During the course of embryonic development the mesocolon of the ascending colon

and descending colon normally fuse with the posterior abdominal wall. Failure of such fusion on the left results in a persistent descending mesocolon. Small bowel may be incarcerated behind such a persistent mesocolon, thus simulating an internal hernia. A characteristic roentgenogram is produced. Abdominal symptoms may at times be severe enough to warrant the performance of a laparotomy and the correction of the anomaly.

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PRIMARY REPAIR OF COMPOUND SKULL FRACTURES IN CHILDREN

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WHILE almost all neurosurgeons agree to the principle of early debridement of compound skull fractures, there are many differences of opinion as to the immediate handling of the bony defect which follows debridement. During a 7 year period at the University of Michigan Hospital 20 children with compound skull fractures have been treated by replacing the free bone fragments as a primary procedure in 19 and by a primary acrylic cranioplasty in 1 patient.

This technique is not without precedent since William MacEwen in 1888 replaced bone fragments after washing them in bichloride of mercury. Coleman, Lyerly, Rowbotham, and Browder also support the idea of early return of bone fragments. Free grafts from the outer table of the skull have been used with excellent results by Gillingham, and primary repair of skull defects by acrylic resin has been described by Schorstein and Reitz.

Primary repair of skull defects should be considered in adults as well as children, but there are certain reasons why in children it is more important to repair these defects at the time of debridement. Such defects are not only undesirable cosmetically but they are a constant source of anxiety to the parents and a potential danger to the patient. These defects are more difficult to repair secondarily in children because of their thin skulls; when prostheses are used they are more apt to loosen or fracture. There is a tendency to procrastinate on the theory that bone regeneration in children is more active than in adults—actually clean defects of the vault more than 1 inch in

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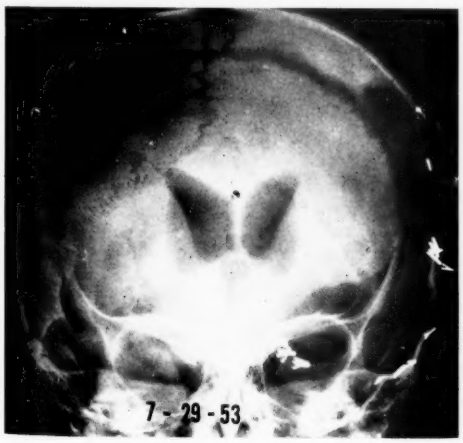
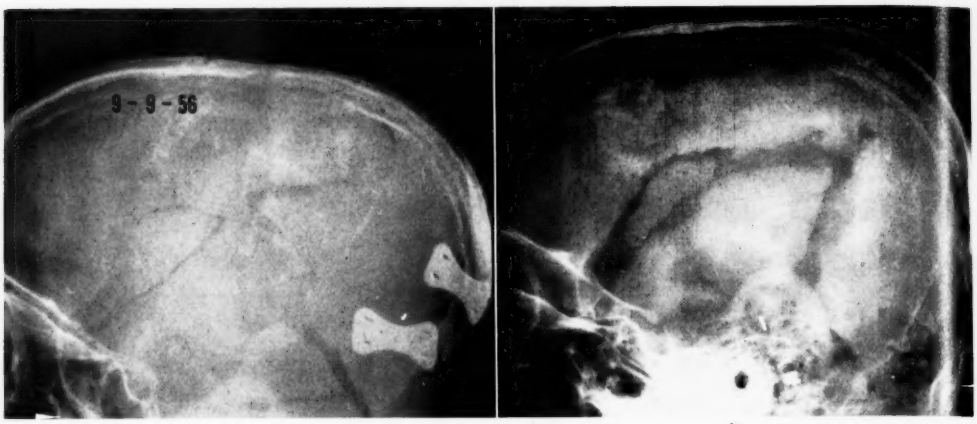


a

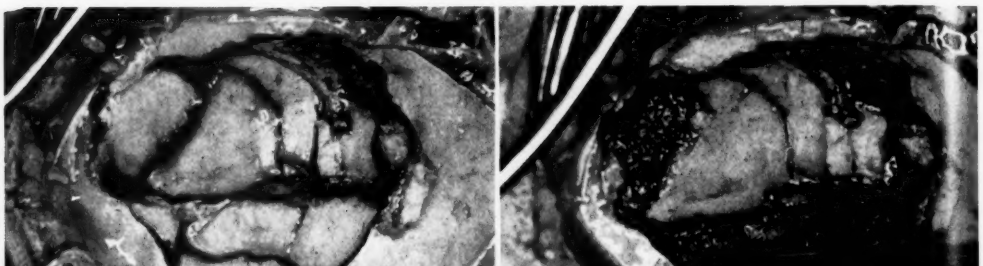
b

FIG. 1. a and b, Ventriculograms made 3 years apart, of the same patient, showing ventricular dilatation occurring beneath a skull defect. Lateral roentgenograms confirm this increase in size.



a b

FIG. 2.



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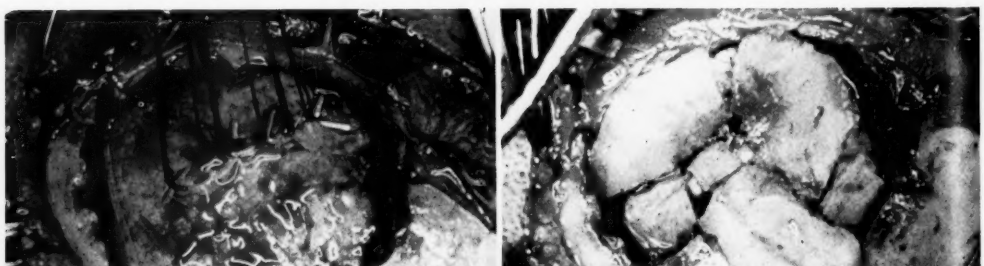
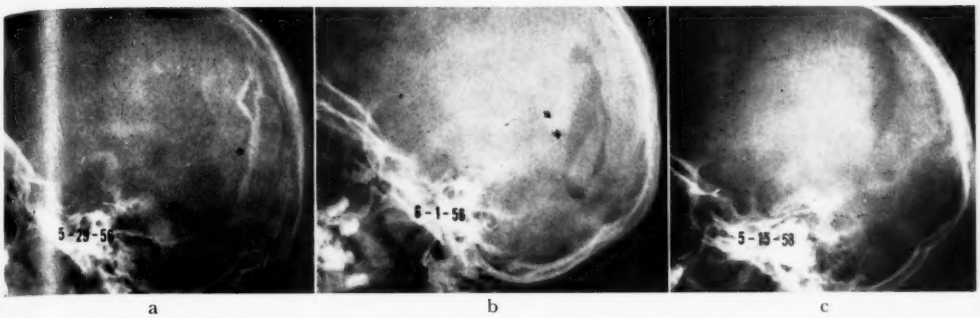


c d

FIG. 3.

FIG. 2. Case 3. a, Preoperative roentgenogram. b, Roentgenogram made 1½ years after replacement of free bone fragments.

FIG. 3. Operative photographs of patient N. A. (Case 18). a, Appearance of undebrided fracture. b, Appearance during debridement showing fragmentation of outer table. c, Dural laceration closed after cortical inspection. d, Bone fragments have been replaced as a mosaic.



a b c

FIG. 4. Case 5. a, Preoperative roentgenographic appearance of depressed left parietal occipital fracture. b, Immediate postoperative roentgenogram showing upper fragment in poor position with its lower border between skull and dura. c, Roentgenogram 2 years later. The dislodged fragment has become absorbed and the free fragments are incorporated.

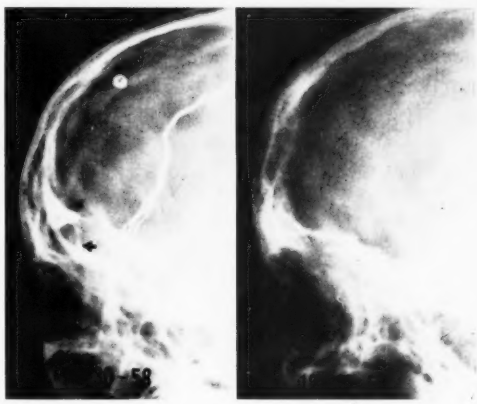
diameter rarely repair themselves in contrast to defects resulting from excision of areas of osteomyelitis. The pulsation of the unsupported brain may lead to cerebral atrophy beneath such a defect with subsequent development of neurologic deficit (Fig. 1) or such defects may contribute to the development of epilepsy due to changes in the hemohydrodynamics of the underlying, unsupported brain, as described by Walker.

CASE REPORTS

Four representative cases are presented in detail with roentgenograms to illustrate the various problems, techniques, and results. A tabulation summarizing all 20 cases is included (Table I).

CASE 3. D. H., Figure 2, a 14 year old left-handed white male, was thrown from a horse striking his head on a plow blade. He was immediately unconscious and was semicomatose upon arrival in the emergency room. Brain was extruding through a 4 centimeter laceration in the left parietal region. Right-sided hemiparesis with a positive Babinski sign was present. Roentgenograms were taken and the patient was operated upon within 5 hours after the accident. The bone fragments from a 10 by 10 centimeter depressed fracture in the left parietal region were all removed and saved (see Fig. 3, Case 18 N. A.). Necrotic brain was removed from a cortical laceration involving the left motor strip through an 8 centimeter dural laceration which was then closed. Several large bone fragments were boiled and replaced in the bony defect. These were held in place by placing periosteal bridges over them, and the scalp was closed in a single layer. The patient remained semicomatose for 2 days postoperatively and then made a rapid recovery with subsidence of the neurologic deficit. He had a seizure involving the face some 5 days postoperatively but has had no subsequent convulsions. Two months after the accident, there was a 3 by 3 centimeter pulsatile defect in the left parietal region but by 9 months after operation this defect was solid. Two and one-half years after the accident this defect is solid, but there is some slight depression present. Neurologically, he is now normal and asymptomatic. His parents report his school work to be at preaccident level, and there is no report of personality change.

CASE 5. J. K., Figure 4, a 6 year old, right-handed white male, was struck by an automobile and thrown 33 feet. On arrival at the emergency room brain was extruding from the left parietal area, but the patient



a b

FIG. 5. Case 17. Roentgenograms of the skull showing: a, The fracture of the supraorbital ridge preoperatively and b, 3 months after the replacement of the ridge.

TABLE I.—SUMMARY OF 20 CASES

Case No. Name Age Sex Date of operation	*Time from accident to definitive repair*	*Type of accident*	*Brain laceration*	*Dural laceration*	*Dural graft*	*Convulsions*		*Size and location of bony defect, cm.*	*Length of follow-up, (mos.)*
						Immediate	*After 3 mos.*		
1. P.R. 8 yrs. M. 6-1-51	3½ mos. old compounding, debris in wound	Struck in R. temporoparietal region with pipe	None	No	No	No	No	2.5 right parietal	94
2. F.L. 10 yrs. M. 12-23-53	8½ hrs.	Struck by truck sleigh riding	None	Yes	No	No	No	R. frontal 6 x 2	84
3. D.H. 14 yrs. M. 9-9-56	5 hrs.	Fell from horse. Struck head on plow blade	Yes—2 x 2 x 8 cm. cortical laceration, facial area	Yes—8 cm.	No	Local facial seizures for 5 days	No	10 x 10 L. parietal	53
4. J.H. 4 yrs. M. 3-31-57	1½ hrs.	Struck by auto	Yes—R. frontal lobe	Yes	No	No	No	2 x 4½ R. Supraorbital ridge	55
5. J.K. 6 yrs. M. 5-29-56	¾ hrs.	Struck by auto, thrown 33 ft.	Yes—necrotic brain	Yes	No	Yes—jacksonian seizures for 7 days	No	2 x 7 L. parietal	55
6. B.F. 11 yrs. F. 1-9-51	5½ hrs.	Struck on head with brick	Yes—necrotic brain removed 2 x 1½ x 1½ cm.	Yes	Yes—periosteum	Yes—4 days. Jacksonian left-sided facial	No	6 x 8 R. parietal	109
7. F.W. 4 yrs. M. 4-29-52	3 days	Auto accident. Dashboard injury	None	Yes	No	No	No	2 x 3 R. supraorbital ridge	84
8. R.S. 10 yrs. M. 4-10-56	5 hrs.	Struck in L. frontal region by golf club	None	No	No	No	No	2 x 3 L. frontal	23
9. J.S. 12 yrs. M. 7-15-56	15 days	Fell out of motor boat, struck by boat	None	No	No	No	No	2 x 2 supraorbital ridge	32
10. M.H. 6 yrs. M. 10-18-55	12 hrs.	Ran into water fountain	None	No	No	No	No	1.5 R. frontal	42
11. C.B. 12 yrs. M. 3-28-54	4 days	Struck on head by golf club	None	No	No	Yes—on O.R. table	No	3 x 2 L. frontal	61
12. J.G. 5 yrs. F. 9-20-52	6 hrs.	Struck by auto	Yes—1 x 1 x 3 cm. in left frontal lobe	Yes	No	No	No	2 x 2 bifrontal	79
13. J.K. 8 yrs. F. 8-1-57	4½ hrs.	Steel object fell off truck, through windshield striking patient	Yes—2 x 5 x 2 cm. L. frontoparietal region	Yes	Yes—1 x 1 cm. periosteal graft	No	No	2 x 6 L. frontoparietal	20
14. J.K. 3 yrs. M. 10-9-54	4 hrs.	Struck on head with armature of electric motor	Yes	Yes	2½ cm. graft	No	No	4 cm. vertex	54

TABLE I.—SUMMARY OF 20 CASES—Continued

Case No. *Name* *Age* *Sex* *Date of operation*	*Time from accident to definitive repair*	*Type of accident*	*Brain laceration*	*Dural laceration*	*Dural graft*	*Convulsions*		*Size and location of bony defect, cm.*	*Length of follow-up, (mos.)*
						Immediate	*After 3 mos.*		
15. S.M. [illegible] yrs. F. 7-[illegible]-54	5½ hrs.	Auto accident	Necrotic cortex removed	No	No	No	No	2 x ½ L. frontal	57
16. G.H. [illegible] yrs. M. 7-[illegible]-57	4 hrs.	Fell from 2nd floor to cement driveway	Yes—necrotic brain removed	Yes	No	No	No	7 x 9 R. frontal	22
17. D.P. 13 yrs. M. 9-30-58	7 hrs.	Auto accident	Yes—frontal lobe debrided 2 x 4 cm.	Yes	Yes—temporalis fascia	No	No	Entire supraorbital ridge	8
18. N.A. 10 yrs. F. 12-17-58	1 hr.	Auto accident	No	Yes	No	No	No	5 x 4½ R. parietal	5
19. J.C. 8 mos. M. 10-26-58	4 hrs.	Shot with 32 caliber bullet, entering and exiting L. parietal region	Yes	Yes	No	No	No	4 x 10 L. parietal	7
20. D.P. 7 yrs. M. 3-31-58	3 hrs.	Auto accident	Yes	Yes	No	No	No	3 x 4 L. fronto-parietal	13

was semiconscious and was moving all four extremities. Roentgenograms were obtained and within 40 minutes of the accident the patient was operated upon and the depressed bone fragments were removed. Necrotic brain was removed, the dural laceration was closed primarily, and the bone fragments were boiled and returned to the defect. These were covered only partially with pericranium bridging from either side of the defect. The bony defect measured 2 by 7 centimeters. Postoperatively, the patient was aphasic and had a right-sided hemiparesis both of which cleared within 1 month of the operation. The patient had a right-sided jacksonian convulsion 7 days after the operation and anticonvulsive medication was begun and administered for 1½ years postoperatively. There were no subsequent convulsions. Two years after the injury there is no neurologic or mental deficit and the area of the fracture is solid.

CASE 17. D. P., Figure 5, a 13 year old, right-handed white male, was involved in an automobile accident. A large laceration was present in the right supraorbital region and brain was extruding through the laceration. The patient was comatose. On exploration 7 hours after the accident, the right supraorbital ridge was found to be depressed into the frontal lobe as a free fragment through a dural defect which measured 2 by 4 centimeters. The roof of the orbit was completely avulsed. The frontal lobe was debrided and the supraorbital ridge removed and placed in saline. The dura was closed with a temporalis fascia graft. The supraorbital ridge was replaced and wired for stability. The patient made an excellent recovery and neurologically was normal at the time of discharge. The supraorbital ridge remained in excellent position, and a fine cosmetic result was obtained. It should be noted that the frontal sinuses were not developed in this young male.

CASE 19. J. C., an 8 month old white male, was shot with a 32 caliber pistol, the bullet entering the left parietal region and exiting through the left frontal region. On admission to the emergency room, the patient was conscious but there was some weakness of the right arm and leg. The patient was operated upon 4 hours after the accident through a transcoronal flap so that both the wounds of entrance and exit of the missile and the fragmented skull between could be visualized (Fig. 6). The bullet tract was debrided, approximately 2 by 2 by 10 centimeters of brain tissue being removed. The bone fragments were removed to gain exposure and were washed in saline. The larger fragments were replaced after the dura was closed. Postoperatively, the patient's neurologic deficit cleared, and there has been no evidence of infection or seizures.

DISCUSSION

All but 2 of the cases at the University of Michigan Hospital were debrided within 2 or 3 days of the accident with replacement of the bone fragments. All patients have been carefully checked postoperatively and pri-

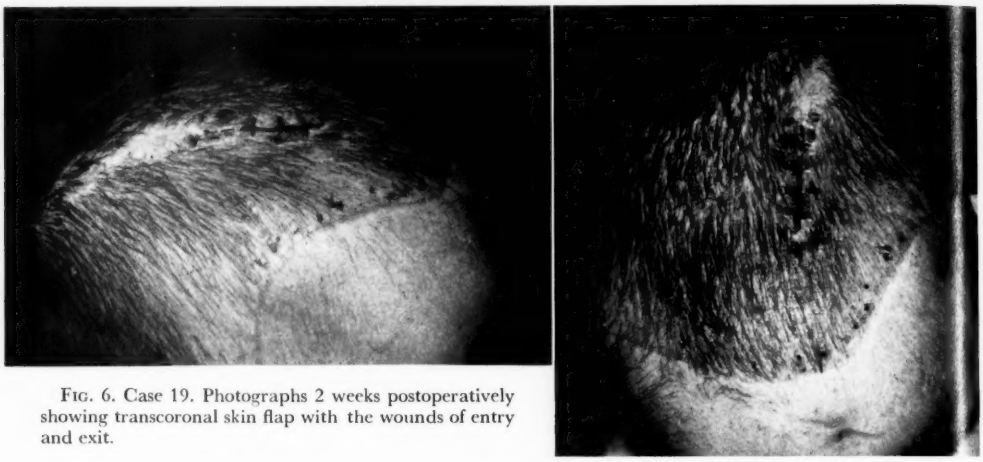


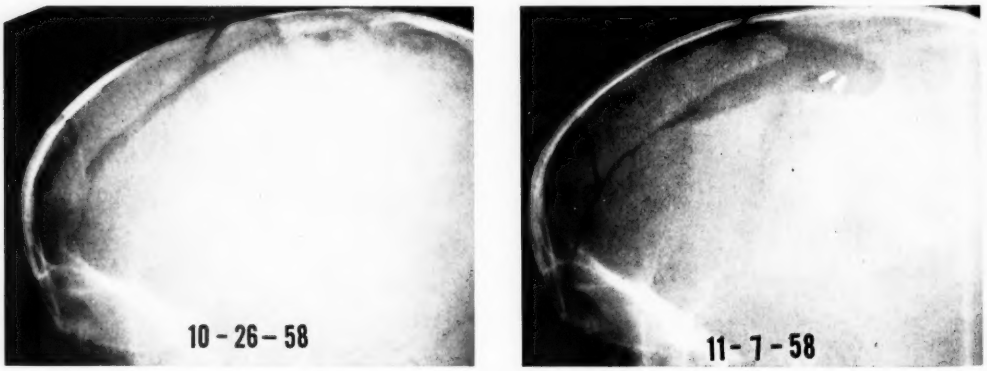
FIG. 6. Case 19. Photographs 2 weeks postoperatively showing transcoronal skin flap with the wounds of entry and exit.

mary healing without pulsatile defect at the site of repair has resulted in all instances. There have been no complications.

Fourteen patients had dural lacerations which were closed primarily or with dural grafts and 12 patients had cortical lacerations with loss of brain tissue. However, in no case has a permanent neurologic deficit resulted. Even in the absence of dural laceration, we advise that a small opening be made in the dura at the time of the primary repair to permit subdural exploration.

Although 3 patients had convulsions in the immediate postoperative period, there have been no subsequent seizures. Epileptic attacks in the immediate postoperative period are generally focal in type, do not necessarily recur, and do not carry the serious import of those which occur subsequently.

These seizures are only expressions of the acute cerebral injury. Walker has pointed out that the incidence of posttraumatic epilepsy is approximately 36 per cent if there has been laceration of the brain and that only one-third to one-quarter of those patients who ultimately develop posttraumatic epilepsy have their first attack after 2



a b

FIG. 7. Case 19. a, Preoperative roentgenogram. Note shattering of the skull. b, Postoperative roentgenogram. Fragments have been replaced.

years. Twelve of our patients who had brain laceration have been traced for from 7 months to 9 years. Since there have been no reported convulsions in any of our patients, it would seem that the incidence of post-traumatic epilepsy may have been reduced in this series.

SUMMARY

The primary repair of compound skull fractures in 20 children using the free bone fragments has resulted in primary healing in all, without pulsatile skull defect or complication. We would stress the necessity of dural closure either primarily or by graft if the bone fragments are to be replaced. The supraorbital ridge has twice been replaced as a free fragment with an excellent cosmetic result. It is believed that the incidence of posttraumatic epilepsy may have been reduced by this procedure.

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IRON-DEFICIENCY ANEMIA IN PREGNANCY

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THE MAINTENANCE of an optimal hemoglobin level has become one of the more important objectives in the care of the pregnant patient. Today, the recognition of anemia occurring during pregnancy has been enhanced greatly because of a better understanding of iron metabolism. Approximately 98 per cent of the anemias occurring during pregnancy are iron-deficiency anemias.

In 4,744 consecutive patients admitted to the Obstetrical Service during the period from 1956 to 1958 inclusive, 852 patients were found to have moderate anemia and 89 severe anemia. In this series, moderate anemia refers to a hemoglobin ranging from 9 to 11 grams per 100 milliliters and severe anemia, less than 9 grams per 100 milliliters, occurring at any time during the prenatal period. Approximately one-third of these patients are from the private service and two-thirds from the ward service. No attempt was made to subdivide the anemic patients into racial groupings. The over-all incidence of moderate and severe iron-deficiency anemia during this period was 20 per cent, of which 2 per cent was severe anemia.

A diagnosis of anemia, in this study, was made when the initial hemoglobin determination or a repeat hemoglobin determination taken during the last trimester of pregnancy fell below 11 grams per 100 milliliters. In view of recent reports from Holly (4, 5), this level is probably too low and the dividing line should be 12 grams per 100 milliliters. Observations during this study substantiate the need of using the higher figure of 12 grams per 100 milliliters hemoglobin as the lower limits of normal during pregnancy.

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Iron-deficiency anemia is only one aspect of the over-all iron-deficiency state in the pregnant patient. Iron is not only an essential component of hemoglobin, but also of myoglobin and many enzyme systems. In the past few years, the use of radioactive iron studies have delineated more clearly the changes occurring in altered iron metabolism.

IRON METABOLISM

A brief review of iron metabolism is necessary for understanding the development of the iron-deficiency state during pregnancy. The total body iron of a normal adult female is approximately 3 to 4 grams, of which 1,800 to 2,400 milligrams are contained in the circulating hemoglobin. Myoglobin contains 10 to 20 per cent and a smaller amount is present in the respiratory enzymes. The remainder (500 to 1,000 mgm.) is stored in the liver, spleen, and bone marrow.

Absorption. The average diet contains 10 to 15 milligrams of food iron, of which 0.5 to 1.5 milligrams are absorbed daily by the normal individual. In subjects with iron deficiency, the ability for iron absorption is enhanced up to 3 to 4 milligrams per day. Ingested iron must be reduced to the ferrous form in the stomach and intestine before it can be absorbed. Iron is absorbed mainly through the mucosa of the duodenum and upper ileum; however, recently, Heilmeyer has shown very good gastric absorption of iron.

The mechanism by which iron is absorbed is not completely understood. According to Granick, individual iron ions can pass through the mucosa directly to the blood stream when only minimal amounts of iron are available from the lumen of the intestinal tract. When increased amounts of

iron are available, the iron enters the mucosa cell by combining with the protein, apoferritin, to form ferritin. Ferritin releases iron directly into the blood stream. Recent studies by Heilmeyer indicate that there is no such thing as a "mucosal block" preventing further iron absorption, but that an unknown regulator of iron uptake exists.

Transport. Iron is transported in the plasma by an iron-binding protein, beta-1 globulin, called transferrin. Normally, there is sufficient transferrin to combine with and transport 9 to 10 milligrams of iron. Ordinarily, only approximately a third of the available transferrin is bound with the total serum iron. Determination of serum iron measures the amount of iron bound to transferrin. The normal range of serum iron is 60 to 200 micrograms per 100 milliliters. The unbound or latent iron-binding protein, transferrin, is termed the latent iron-binding capacity. The average latent iron-binding capacity is approximately 185 micrograms per 100 milliliters with a normal range of from 100 to 200 micrograms per 100 milliliters. The total iron-binding capacity is equal to the sum of the serum iron value and the latent iron-binding capacity value. The total iron-binding capacity indicates the total amount of iron that can be bound by the transferrin in the serum.

Storage. The main sites of iron storage are in the liver, spleen, and the bone marrow. Iron is stored in the cells as ferritin or hemosiderin. Although ferritin is more differentiated than hemosiderin, both forms are available for hemoglobin synthesis when the need arises. The factors regulating the amount of stored iron are absorption and excretion of iron and the amount of hemoglobin circulating. The only practical method for determining the amount of storage iron is staining aspirated marrow for iron. Normally, the amount of iron in storage is 40 per cent of that in hemoglobin, approximately 1,000 milligrams of iron. Holly (5) has shown that iron-deficiency anemia does not occur until after the iron in storage is completely depleted, and, conversely, iron storage is not replenished until after the hemoglobin has reached its normal level (above 12 gm./100 ml.).

Erythropoiesis. The main pathways of normal serum iron exchange are from serum to marrow to erythrocytes and then, after destruction of the erythrocyte, back to serum. It has been estimated that more than 90 per cent of the iron leaving the serum enters erythropoietic marrow and only two-thirds of this iron is utilized for hemoglobin formation. The remainder returns to the serum. In the marrow, the iron is combined with erythrocyte protoporphyrin within the red cell to form hemoglobin. The measurable erythrocyte protoporphyrin is the amount of unbound porphyrin in the erythrocyte and, in the normal patient, ranges from 20 to 50 gamma per cent. A small fraction of the hemoglobin mass is destroyed and replaced each day. This iron from hemoglobin breakdown is liberated into the serum and made available to the marrow for new hemoglobin formation. Recent studies by Pollycove indicate that 25 to 30 milligrams per day of iron are used for hemoglobin synthesis and that the mean life span of erythrocytes in normal subjects is approximately 120 days. In patients with iron-deficiency anemia, the life span of the erythrocyte is considerably reduced (a 30 to 60 day life span). As a result of the shortened life span of the poorly hemoglobinized red cells in the iron-deficiency state, the marrow is hyperplastic.

Excretion. The amount of iron excreted is small—from 1 to 1.5 milligrams per day. These losses are from the urine, the gastrointestinal tract, and sweat. Approximately 15 to 30 milligrams of iron are lost each month by the average menstrual flow. This added loss of iron by the menses keeps the female in a precarious state of iron balance and accounts for the higher frequency of iron-deficiency anemia occurring in women.

Iron transport to the fetus. Iron is delivered to the placental villi by maternal transferrin, and the transferrin in the fetal blood

TABLE I.—IRON BALANCE IN PREGNANCY

	Iron requirement, mgm.
Fetus and placenta	400
Increased red blood cell mass	500
Blood loss at delivery	100
Excretion	200
Total	1200
Iron absorption	500
Deficit	700

TABLE II.—EXAMPLE OF HEMATOLOGIC VALUES

Morphologic	
Hemoglobin	10 gm./100 ml.
Hematocrit	30 per cent
Red blood cells	3,500,000/mm.^{3}
Mean corpuscular hemoglobin concentration value	33 per cent
Biochemical	
Serum iron	30 mcgm./100 ml.
Iron-binding capacity (transferrin level)	380 mcgm./100 ml.
Erythrocyte protoporphyrin	100 mcgm./100 ml.

conveys iron from the placenta to the fetus. The exact mechanism for transfer of iron across the placenta is not known. Maternal injection of radioactive iron rapidly appears in the fetal blood, within a matter of minutes. In spite of the higher fetal serum iron than the maternal serum iron, the direction of iron transfer is only toward the fetus. It is assumed that this one-way transfer against a gradient is due to the fetal need, since the iron uptake is proportional to the fetal weight. The term fetus and placenta require approximately 400 milligrams of iron. The largest amount of iron is required by the fetus during the last trimester of pregnancy—approximately 310 milligrams of iron. Daily iron requirements of the fetus are estimated to be 1 milligram per day for the first trimester and 2 milligrams for the second trimester. Because of the rapid fetal growth in the last trimester of pregnancy, this fetal demand is increased to 4 milligrams per day (Fig. 1).

Many women enter pregnancy in a precarious state of iron balance. The iron reserve or storage already has been reduced or absent because of the additional loss of 15 to 30 milligrams of iron each month from the menstrual blood. During pregnancy, the demand for iron by the fetus, placenta, and increasing blood volume of the mother is sufficient to produce anemia when iron storage is low or absent. Iron balance during a normal pregnancy is illustrated in Table I. The additional demands for iron upon the mother amount to approximately 1,200 milligrams during the entire pregnancy and, during this same period of time, approximately 500 milligrams of iron are absorbed from a normal diet. This leaves an iron deficit of approximately 700 milligrams. If the maternal iron reserve is adequate, this amount of iron is readily mobilized and converted into hemoglobin. However, if iron storage is low or absent, this iron deficit manifests itself by an iron-deficiency anemia in the mother.

The studies by Holly (4) have shown that the anemia which formerly has been considered "physiological" is actually produced as a result of an iron-deficiency state. In the normal pregnancy, approximately 500 milligrams of iron are needed for additional hemoglobin formation if the red cell mass is to increase proportionately with the increased plasma volume. Coleman has shown that the bone marrow is capable of doubling its rate of hemoglobin production if sufficient iron is supplied. Therefore, if sufficient amounts of iron are made available to the maternal marrow, the patient can maintain her hemoglobin and hematocrit values throughout pregnancy.

DIAGNOSIS

The diagnosis of iron-deficiency anemia in pregnancy is occasionally difficult, especially if the anemia is not marked and of only a few months' duration. Formerly, the diagnosis of anemia was made only after the typical morphologic changes occurred. The majority of patients with mild and moderate iron-deficiency anemia in pregnancy have a normocytic and normochromic blood picture. Finch (8) has stated that the characteristic red cell changes in iron deficiency are a late manifestation and occur months after reserve iron is used.

The early changes of this anemia during pregnancy are the biochemical alterations (iron-binding capacity, serum iron, erythrocyte protoporphyrin values). In Table II, an example of the hematologic values taken in 1 patient during pregnancy illustrates the early biochemical changes as compared to the late morphologic changes. In this patient, the mean corpuscular hemoglobin concentration value is still in the normal range in spite of the iron deficiency. Abnormally high transferrin levels are found in iron-deficiency anemias. Laurell noted that the iron-binding capacity is increased before a subnormal serum iron value occurs. In iron-deficiency anemia of pregnancy, the iron-binding capacity is above 250 micrograms per 100 milliliters, the serum iron falls below 60 microgram per 100 milliliters and the erythrocyte protoporphyrin values are above 60 micrograms per 100 milliliters. These biochemical alterations occur when the hemoglobin falls below 12 grams per 100 milliliters and the hematocrit below 37 per cent.

Since most clinicians do not have access to these biochemical determinations, the diagnosis of iron-deficiency anemia in pregnancy can be assumed to occur when the hemoglobin and hematocrit are below these arbitrary values. In severe anemia (below 9 gm./100 ml. hemoglobin), further investigation, such as biochemical determinations and bone marrow biopsy, is indicated.

TREATMENT

The treatment of iron-deficiency anemia is iron. This statement seems rather trite but it is worth repeating, when one considers the vast number of multiple "hematinics" offered to the physician. To date, there has been no clear evidence of the increased efficacy of iron salts in a combination of vitamins, specifically B_{12} and folic acid. Cobalt in combination with iron may induce an increase of the hematocrit value, but the difference in the hematocrit over that produced by iron salts alone is not important. Several clinicians believe that cobalt has no

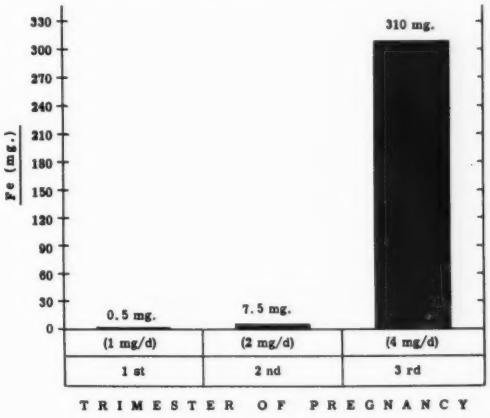

FIG. 1. Iron requirements of fetus.

place in the treatment of iron-deficiency anemia. It has been demonstrated that persons with gastric achlorhydria absorb iron normally and, as a result, these patients do not need hydrochloric acid nor ascorbic acid to supplement the iron therapy. These comments only serve to emphasize that iron alone is the proper treatment for iron-deficiency anemia.

In iron-deficiency anemia occurring during pregnancy, the main therapeutic considerations are (1) the calculation of an adequate dose of iron needed, (2) the route of administration, and (3) the duration of therapy. Of the many methods for calculating the total amount of iron required, the formula suggested by Holly (5) is preferred by the author:

$$\frac{13.5\text{—Pt. Hgb.}}{100} \times 4{,}000 \times 3.4 + 500 = \text{mgm. iron required}$$

In this formula, 4,000 is the average blood volume and 3.4 is the conversion factor from grams of hemoglobin to milligrams of iron. An additional 500 milligrams of iron are added to replenish the iron reserves. It is not adequate to restore only the hemoglobin to normal level, but it is also necessary to supply sufficient iron to replace the iron stores.

There are two routes of administering

iron, oral or parenteral. The preferred method is by the oral route if possible. The well known oral salts, ferrous sulfate and ferrous gluconate, are still unsurpassed both in effectiveness and low cost. From 10 to 15 per cent of the iron is absorbed when given in amounts of from 80 to 150 milligrams per day. Larger sources of oral iron will not materially increase its absorption and will be likely to cause irritability of the gastrointestinal tract. Once anemia is corrected, the mucosal absorption of iron salts is greatly reduced and it takes months to reconstitute iron stores by this route.

The chief indications for the use of parenteral iron in the prenatal period are intolerance to oral iron or a limited time for correcting the iron deficit before the onset of labor. It is stated that approximately 10 to 20 per cent of patients receiving oral iron have severe enough gastrointestinal complaints to interfere with the oral treatment. If the oral iron is started during the early months of pregnancy, usually sufficient time remains for restoring the iron deficit. However, to begin oral iron in the eighth or ninth month of gestation does not allow sufficient time for adequate iron absorption before delivery. In these instances, the intramuscular route of administration is indicated. The preferred intramuscular iron preparation is iron-dextran. This iron preparation can be given in doses of 100 to 500 milligrams daily. Usually, adequate parenteral iron will produce a hemoglobin increase of approximately 2 grams within 14 to 20 days. From recent reports on the use of iron-dextran, it appears to be the agent of choice for parenteral use. Because of the relative absence of toxic effects from iron-dextran, the importance of calculating the total amount of iron required is apparent to prevent the danger of iron overloading. It has been suggested that no more than 3,000 milligrams of iron-dextran should be administered during any one course of treatment for iron-deficiency anemia.

SUMMARY

The most common complication associated with pregnancy is iron-deficiency anemia. In this series of patients, 1 out of 5 patients was found to have a moderate or severe type of iron-deficiency anemia. When the maternal hemoglobin falls below 12 grams per 100 milliliters, iron stores are depleted and the need of iron therapy becomes apparent. Oral iron started early in pregnancy adequately supplies iron requirements during pregnancy. The indications for using parenteral iron are limited to those patients who develop an intolerance to oral iron or in those patients who have an iron-deficiency anemia occurring late in the pregnancy.

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GIGANTOMASTIA COMPLICATING PREGNANCY

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HYPERTROPHY of the breasts in pregnancy is a natural phenomenon which may be converted on rare occasions into both a medical and scientific curiosity by the development of gigantomastia. This term denotes a diffuse, progressive, massive and frequently incapacitating enlargement of the breasts associated with pregnancy. This condition undoubtedly represents an abnormal response to physiologic stimulation. True gigantomastia develops rapidly during pregnancy, undergoes regression after delivery, and recurs with subsequent pregnancies.

In the experience of The Johns Hopkins Hospital during the last 25 years there have been 2 cases in 56,794 deliveries.

HISTORICAL REVIEW

Deaver and McFarland analyzed 240 cases of mammary hypertrophy collected from the literature and decided that only 182 represented true hypertrophy. In 35 of these cases the patient was seen for the first time during pregnancy because of an exacerbation of the breast hypertrophy. In only 29 patients of this group does the history suggest true gigantomastia, with gross enlargement in successive pregnancies. The earliest of these was reported by Palmuth in 1648, with the description "both breasts enlarged in every pregnancy and the axillary glands swelled to the size of a child's head." Van Swieten described a similar case in 1746, in which the breasts subsided after each lactation period. Rosinski observed 1 patient through 4 pregnancies, with spontaneous regression after each period of lactation. In many of the patients analyzed by Deaver and McFarland, bilateral breast amputation was performed both in the virginal hypertrophy and in the pregnancy group. Thus the patient's response to a subsequent pregnancy could not be determined, nor the possibility of a slow but spontaneous regression of the gigantomastia. Surgical intervention was usually deemed necessary for mechanical reasons, either because of difficulties with ambulation, or because of local changes in the breasts due to excessive weight and circulatory impairment, with ulceration, sloughing, hemorrhage, and infection. As recently as 1920 Simpson reported the death of a 32 year old primipara early in pregnancy from sloughing and secondary infection of markedly enlarged breasts.

Bankoff has reported a series of 6 patients suffering from primary sterility or repeated abortions, in whom at least 1 successful pregnancy followed mammoplasty for breast hypertrophy. One of the 2 patients described by Burslem and Dewhurst was followed through 2 successive pregnancies, with minimal postlactation regression; this patient was treated unsuccessfully with stilbestrol after her second delivery. In 1957 Williams reported a patient observed through 2 pregnancies; bilateral amputation of the breasts was performed early in the first pregnancy. Gross enlargement and ulceration of supernumerary breasts in the axillae necessitated their operative removal in the second pregnancy in spite of testosterone therapy. Both testosterone and progesterone therapy were used unsuccessfully by Blaydes and Kinnebrew in their 1 patient, but amputation became necessary because of massive hemor-

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rhage. Endocrine studies conducted on this patient were inconclusive.

Deaver and McFarland felt sure that breast hypertrophy resulted from a blood borne disturbance that was probably endocrine in origin. Since then the isolation of the ovarian hormones, and more recently of the pituitary group, has clarified the pattern of breast development. Although breast development may appear in infancy and childhood, significant changes usually appear only with the onset of puberty. Undoubtedly, the bulk of the tissue is adipose, but there is a gradual downward growth of ducts from the nipple anlage with the formation of glandular elements. The hormones principally responsible for breast development are prolactin, or the mammotropic hormone, and the ovarian hormones, estrogen and progesterone. All three are essential for normal development. However, it appears that somatotrophin, or the pituitary growth hormone, is also mammogenic in action and, in addition to increasing body weight, seems to cause even more intense mitotic activity and duct proliferation than prolactin and estrogen alone. It is of special interest in this study to note that high concentrations of at least three of these hormones (estrogen, progesterone, and mammotropin) and possibly somatotrophin are produced in the placenta. Prolactin itself has a three-fold action—mammotrophic, luteotrophic, and lactogenic—and so is essential in the differentiation of alveolae and lobule formation in synergism with progesterone. All phases of breast development and activity proceed more normally in the presence of adrenal hormones, stimulated by corticotrophins.

This normal pattern of breast development is dependent not only on a continuing supply of hormones but also on efficient handling of these substances by the liver. Zondek, in 1934, suggested that the inactivation of steroids took place in the liver. Evidence has since accumulated from animal experiments to indicate that most phases of the metabolism of the sex steroids occur in the liver prior to both utilization and excretion. Folic acid, which is essential for the tissue growth functions of estrogens, is stored in the liver. Normally, the liver has a wide margin of safety and gross damage must be present before there is clinical evidence of disturbed steroid metabolism. However, current concepts concerning corticoid metabolism in pregnancy make it appear altogether possible that the liver glucuronic acid conjugating mechanism may be so overtaxed after the first trimester (even in normal pregnancy) that it becomes inefficient.

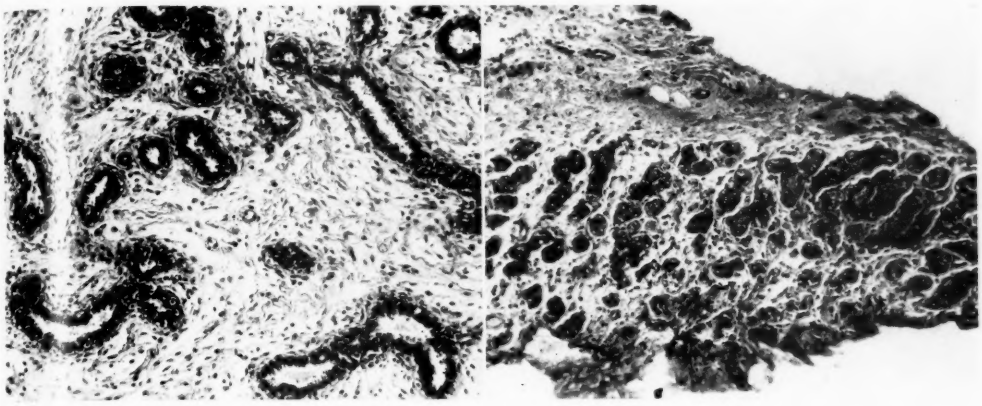
ETIOLOGY

There are a few scattered reports of breast hypertrophy occurring in more than one member of a family, but scarcely enough to suggest a true familial predisposition.

Growth of the breasts, whether at puberty or during pregnancy, is the direct result of hormone stimulation, and the resultant size depends on the responsiveness of each individual mammary gland. Geschickter found that the administration of estrogens to patients with virginal or gravid hypertrophy led to further enlargement of the breasts. He believed that breast tissue possessed an innate self-limitation of responsiveness which is absent in patients with hypertrophy, and he was unable to block the effect of intense estrogen stimulation in these patients either with testosterone or the lactogenic hormone.

PATHOGENESIS

Microscopic examination of breasts removed late in pregnancy usually shows some lactogenic effect. However, the most striking change is the tremendous hypertrophy of connective tissue which is considerably in excess of the glandular hyperplasia. Normally two types of connective tissue are present in the breast: (1) the fibrous supporting connective tissue which usually contains fat and separates collections of lobules from each other and which takes no active part in breast changes; and (2) the intralobular connective tissue which may be either periductal or periacinar and which is responsive to hormone stimulation. This



a b

FIG. 1. a, b, Microscopic sections of patients T. T. and S. F. showing acinar and periacinar connective tissue stroma proliferation associated with pregnancy. The fibrous tissue stroma appears to be edematous and fluid containing.

tissue increases in states of normal breast activity, as at puberty and in pregnancy. Normal stroma cells resemble small fibroblasts, and usually small fibrils are present in the tissue. Moskowicz was the first investigator to observe cyclic changes in breast stroma. He found edema of the periductal and periacinal connective tissue in the premenstrual phase, with a wide-meshed reticular arrangement of fibrils. Later in the cycle this tissue becomes thicker and more compact. Ratzenhofer has recently described the presence of microscopically demonstrable amounts of free fluid, with a high protein content, in the interstitial tissues, during pregnancy and the menstrual cycle. He found that the persistence of this fluid in patients with hormone imbalance led to a change in the proteins and to the synthesis of solid mucopolysaccharides. Of special interest in this connection are the histochemical studies of breast stroma of Ihnen and Perez-Tamayo, and more recently of Fisher and Creed. In the periductal stroma of patients with gynecomastia these latter investigators were able to identify a ground substance which proved to be a mucopolysaccharide presumably identical with hyaluronic acid. A substance with similar metachromatic properties was isolated in fibroadenomas, and with less intensity in normal female breast tissue. This same substance has been isolated, after estrogen stimulation, in other connective tissue, such as the sex skin of the monkey, which is responsive to hormone stimulation. It seems highly probable that similar changes occur in the stroma in gigantomastia (Fig. 1a and b) and that one is dealing with abnormal retention in the tissue spaces.

CASE REPORTS

CASE 1. T. T., an 18 year old unmarried negro female, was first admitted to the obstetrical service of The Johns Hopkins Hospital on September 10, 1947, because of marked enlargement of both breasts associated with her first pregnancy. Her serologic test for syphilis was negative and she was Rh positive. In August 1947, when 6 months pregnant, she first noted rapid breast enlargement associated with pain and tenderness. When she entered the hospital, the circumference of the right breast was 67 centimeters, and the circumference of the chest was 105 centimeters. All roentgenologic and laboratory studies were negative except for a slight anemia (hemoglobin, 11 gm.). A biopsy of the right breast revealed "lactating breast" (Fig. 1b). The patient received massive doses of stilbestrol (7,640 mgm. in 18 days) without benefit to her enlarged breasts; clinically she appeared worse. The circumference of the chest actually increased to 107 centimeters. She was discharged from the hospital on October 5, 1947. Urinary pregnanediol assay on September 12, 1947 was 3.8 milligrams per 24 hours (normal average 40 grams per 24 hours, low 30 milligrams per 24 hours), and on October 4, 1947 it was

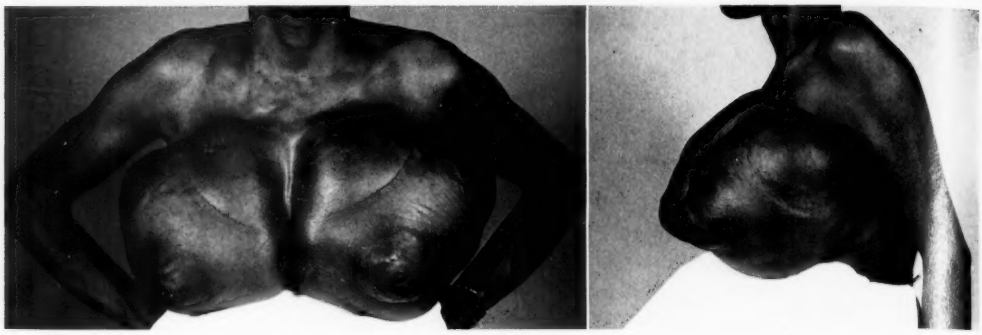


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FIG. 2. a, b, Patient T. T. during ninth month of her third pregnancy. Circumference of chest measured 112.5 centimeters.

28.8 milligrams per 24 hours (normal average 50 milligrams per 24 hours, low 40 milligrams per 24 hours).

While being observed in the prenatal clinic, the breasts became progressively larger. The patient was readmitted to the hospital on November 12, 1947. The circumference of the chest was 113 centimeters; right breast 73 centimeters, and left breast 80 centimeters. Laboratory studies revealed a severe anemia (hemoglobin 6.0 gm.). After transfusions she was delivered by elective low forceps of a 2,450 milligram normal female child on November 25, 1947. On the second postpartum day, the breasts increased in size and the circumference of the chest was 121 centimeters. The patient was in agonizing pain and the tense skin of the breasts started to ulcerate. A short course of testosterone therapy was of no benefit. Morphine and ice caps provided some palliative relief. Breast feeding was attempted but was unsuccessful. The postpartum course became febrile and despite penicillin therapy, the temperature rose to 102 degrees F. at night. The patient became lethargic and semiresponsive. Her pulse was weak, her skin was cold and her respirations were rapid and shallow. Although urinary output was adequate the nonprotein nitrogen rose to 100 milligrams per cent, and the chlorides were 82 milliequivalents per liter. Her condition remained shock like and critical for several days. Both breasts were markedly engorged and exquisitely tender.

On December 5, 1947, an ill-defined tender mass was noted in the right upper quadrant of the abdomen. The white blood count was elevated to 20,500 but all other laboratory tests were negative. Sulfadiazine was added to her therapy and her general condition gradually improved. On December 12, 1947 her chest circumference had regressed to 105 centimeters.

On January 9, 1948, the circumference of the chest was 98 centimeters and the breasts were nodular, enlarged, and tender. A mass in the right upper quadrant was still present but thought to be the liver. Laboratory studies were essentially negative except for the glucose tolerance curve which was flat. Biopsy of breast and right axillary node revealed chronic breast abscess, lactating breast, and hyperplastic lymph node. On January 20, 1948, the circumference of the chest was 95 centimeters, left breast 64 centimeters, and right breast 64 centimeters. She was discharged on January 24, 1948.

The patient was next admitted to the University of Maryland Hospital on February 1, 1950 in active labor. The prenatal course was complicated by bilateral enlargement of the breasts for which she was under observation. Chest circumference on December 14, 1949, was 106 centimeters, and on January 25, 1950, it was still 106 centimeters. There was a spontaneous delivery of a normal male child. On the third postpartum day the breasts became much larger, extremely painful, and her temperature rose to 103 degrees F. Analgesics were of slight benefit. Penicillin and aureomycin were given. The temperature elevation gradually subsided and the breasts slowly regressed in size. The patient was discharged on February 10, 1950. Breast feeding was not attempted. The patient stated that the breasts returned to "normal size" in about 8 weeks.

She was next seen February 17, 1953, at the Sinai Hospital when she was 6½ months pregnant. The breasts were again markedly enlarged. On April 1, 1953 the circumference of the chest measured 112.5 centimeters, and the circumference of right breast was 65 centimeters. (Fig. 2a and b). Patient was given 100 milligrams of testosterone propionate intramuscularly 3 times a week for 4 weeks until delivery, with no change in the size of the breasts. Spontaneous delivery occurred on April 28, 1953. The postpartum course was marked by engorgement of both breasts, pain, and temperature elevation. Testosterone propionate and terramycin were administered. Bilateral tubal ligation and appendectomy were performed prior to discharge on May 19, 1953. The breasts returned to "normal" size in about 2 to 3 months (Fig. 3).

CASE 2. S. F., a 20 year old married negro female, was first admitted to the obstetrical service in March 1954. Her serologic test for syphilis was negative and she was Rh negative (no antibodies). She spontaneously delivered her second child, a 3,800 gram normal female who was breast fed and is at present alive and well. Hypertension developed during the postpartum period, but the patient had no difficulty with excessive breast enlargement.

Her next pregnancy was in 1955 at which time a normal male infant was delivered at Baltimore City Hospital. No complications were noted.

In December 1956 this patient was 3 months pregnant when she was first operated upon at The Johns Hopkins Hospital because of an excessive enlargement of the left breast. The pathology report revealed a giant fibroadenoma. Within 3 weeks after her hospital discharge, the patient was readmitted to the surgical service because of pain, redness, and progressive swelling of the left breast. Some discharge was noted from the previous biopsy incision, and a marked enlargement of the inframammary accessory breast on the left was present. The right breast was enlarged but not to the same degree as on the left. Surgical excision of the accessory left breast was performed on December 24, 1956.

She was followed in the breast and obstetric clinics for gigantomastia complicating pregnancy. From January to April 1957 the circumference of the left breast increased from 53 to 80 centimeters; the right breast from 53 to 63 centimeters. She was admitted to the obstetrical service April 4, 1957, for observation and study. Significant findings revealed marked hypertrophy of both breasts, particularly on the left (Fig. 4). There was extensive nodularity which was soft and nontender. The vascular markings were greatly increased and there was evidence of edema of the dependent portion of both breasts. The abdomen showed a symmetric swelling with the fundus above the umbilicus. There was moderate peripheral edema. Laboratory studies revealed a marked anemia with a hematocrit of 26.9 per cent, hemoglobin of 7.0 grams, and red blood cell count of 2,940,000. There was a normal white blood cell count and differential. The urine was normal as were the chemistry values for nonprotein nitrogen, sugar, cholesterol, phosphorus, alkaline phosphatase, and protein-bound iodine. The bilirubin was less than 0.8 milligram per cent, the cephalin flocculation was 1 plus, and the thymol turbidity was slightly elevated to 7.2 units. The total serum protein was 7.4 grams per cent, but the albumin was 3.1 grams per cent and globulin 4.3 grams per cent ratio was reversed. The urinary estrogen assay was elevated but not consistent with the duration of pregnancy:

		Limits of normal values:
Estrone	0.06 mgm./24 hrs.	0.4– 1.5 mgm./24 hrs.
Estradiol	0.04 mgm./24 hrs.	0.1– 0.4 mgm./24 hrs.
Estriol	2.30 mgm./24 hrs.	7.0–15.0 mgm./24 hrs.
Total estrogens	2.40 mgm./24 hrs.	

FIG. 3. Patient T. T. 2 years after her last pregnancy showing remarkable regression of gigantomastia.

4-6-57	Pregnanediol 12.8 mgm./24 hrs.	(aver. 33 mgm./24 hrs., low 20 mgm./24 hrs.)
4-11-57	Pregnanediol 13.4 mgm./24 hrs.	(aver. 40 mgm./24 hrs., low 30 mgm./24 hrs.)
17-Ketosteroid	2.74 mgm. (normal 7–15 mgm./24 hrs.)	
a-ketonic	2.14 mgm.	

No characteristic patterns.

The patient was transfused and given iron therapy and discharged to the breast clinic where she received 50 milligrams of testosterone propionate intramuscularly 3 times a week. During the next 2 months the patient continued on testosterone therapy with little or no further change in the size of the breasts.

On re-examination just prior to delivery the following hormone assays were obtained:

Pregnanediol	21.8 mgm./24 hrs. (aver. 65 mgm./24 hrs., low 23 mgm./24 hrs.)
17-Ketosteroids	12.5 mgm./48 hrs. (method of Dobriner)
a-ketonic fraction	9.4 mgm./48 hrs.
Androsterone	1.8 mgm./48 hrs.
Etiocholanolone	1.68 mgm./48 hrs.

No recognizable patterns otherwise.

On June 11, 1957, the patient delivered a normal 2,870 gram female child with normal genitalia and no enlargement of the clitoris. Results of all blood chemistry studies were normal including the 17-ketosteroid value of 5.13 milligrams per 24 hours. Testosterone therapy was continued for 1 month post partum and the breasts regressed slowly. Physical examination in June 1957 revealed multiple areas of hypertrophy and nodularity with soft axillary adenopathy present on both sides. Tubal ligation was advised but refused by the patient. Examination on November 6, 1957, revealed that the breasts had almost returned to normal size and consistency.

On April 9, 1957, the patient was examined in the breast clinic and found to be 3 months pregnant. The breasts again were enlarged with an "orange-sized

tumor" present on the left (Fig. 5). She was admitted to The Johns Hopkins Hospital on April 21, 1958 for endocrine evaluation. Special studies revealed 11.1 grams of hemoglobin, hematocrit 36.4 per cent, white blood cells 5,800, normal differential count, nonprotein nitrogen 23 milligrams per cent, cholesterol 225 milligrams per cent, total protein 7.6 grams per cent, albumin 3.8 grams per cent, globulin 3.8 grams per cent, urine, blood volume normal, hemoglobin electrophoresis normal and liver function tests normal. The following hormone assays were performed on blood and urine:

		Normal values: Average	Low
Pregnanediol			
4-25-58	14.7 mgm./24 hrs.	19 mgm./24 hrs.	10 mgm./24 hrs.
4-27-58	7.4 mgm./24 hrs.	19 mgm./24 hrs.	10 mgm./24 hrs.
4-29-58	8.0 mgm./24 hrs.	19 mgm./24 hrs.	10 mgm./24 hrs.
17-Ketosteroids			
4-24-58	3.84 mgm./24 hrs.	10 mgm./24 hrs.	5 mgm./24 hrs.
4-25-58	2.2 mgm./24 hrs.	10 mgm./24 hrs.	5 mgm./24 hrs.
5-1-58	3.75 mgm./24 hrs.	10 mgm./24 hrs.	5 mgm./24 hrs.
Androsterone	2.07 mgm./24 hrs.		
Etiocholanolone	1.23 mgm./24 hrs.		
4-25-58	Growth hormone (blood)	520 mcgm./100 ml. plasma (280–295 mcgm./100 ml.)	
5-1-58	Progestin (blood)	.6 eq./ml. of plasma.	
5-1-58	Prolactin (urine)	206 I.U./24 hrs.	

		Average	Low
17-Hydroxycorticosteroids (urine)			
4-24-58	1.42 mgm./24 hrs.	17.5 mgm./24 hrs.	4.5 mgm./24 hrs.
17-Hydroxycorticosteroids (plasma)			
4-28-58	5.4 mcgm./100 ml. plasma	6–12 mcgm./100 ml.	

			Average values:
Urinary estrogens (method of Brown)			
4-25-58	Estrone	0.27 mgm./100 c.c.	0.1 –0.2 mgm./100 c.c.
	Estradiol	0.07 mgm./100 c.c.	0.06–0.1 mgm./100 c.c.
	Estriol	2.80 mgm./100 c.c.	1.0 –2.0 mgm./100 c.c.
	Total	3.13 mgm./100 c.c.	
Estrone			Average values:
4-27-58	Estrone	0.02 mgm./100 c.c.	0.2 –0.4 gm./100 c.c.
	Estradiol	0.1 gm./100 cc.	0.08–0.15 mgm./100 c.c.
	Estriol	0.69 mgm./100 c.c.	1.5 –3.0 mgm./100 c.c.
	Total	0.72 mgm./100 c.c.	
4-29-58	Estrone	0.01 mgm./100 c.c.	0.2 –0.4 mgm./100 c.c.
	Estradiol	0.01 mgm./100 c.c.	0.08–0.15 mgm./100 c.c.
	Estriol	0.61 mgm./100 c.c.	1.5 –3.0 mgm./100 c.c.
	Total	0.63 mgm/100 c.c.	

The salicylic acid conjugation test of liver function was performed April 30, 1958, when the patient was about 3½ months pregnant. The results indicated a decreased ability of the liver to conjugate salicylic acid. A normal pregnant patient served as the control. After delivery this salicylic acid conjugation test was repeated and found to be normal. The results were as follows: 51.2 per cent glycine, 21.7 per cent glucuronide, 60 per cent of glucuronide fraction as acyl, and 27.1 per cent free.

On May 2, 1958, the patient was placed on 17-alpha ethinyl-19-nortestosterone (norethindrone), 20 milligrams a day. This compound is an oral progestational agent. During the next 4 months the patient continued on norethindrone therapy receiving 20 milligrams daily. The measurements of the breasts showed no further increase in size during the remainder of pregnancy while the patient was receiving this drug (Figs. 6 and 7).

		Greatest circumference, cm. Chest	Left Breast
6- 4-58		104	53
7-23-58		102	52
8- 6-58		106	54
8-27-58		112	53
9-10-58	Norethindrone stopped.		
10- 8-58		114.5	59
10-10-58	Delivery of a 3030 gm. normal male infant without complications.		
10-14-58		117	59
Testosterone proprionate 50 mgm. I.M. q.d. for 1 week			
11- 5-58		93	46
12- 3-58		94	42

A few weeks after delivery the newborn infant developed pneumonia and was treated intensively with antibiotics. This therapy was unrelated to norethindrone therapy.

On November 17, 1958, the patient was admitted to the hospital for tubal ligation. Section of the right ovary was examined and found to be normal. All laboratory studies were considered normal including urine analysis, Fishberg test, electrocardiograms, roentgenograms of the chest, blood counts, and blood chemistry examinations. Liver function studies were essentially normal (including a salicylate conjugation test).

DISCUSSION

In a review of the available laboratory studies made during previous pregnancies complicated by gigantomastia, it was apparent that the urinary steroid metabolites, pregnanediol, estrogens, and 17-ketosteroids, were low. However, as the values were obtained from specimens collected after the onset of the breast hypertrophy and at such times when the patients were chronically ill, there was some question as to the interpretation of the results. Therefore, it was fortunate that a study of the steroid hormone excretion could be made in the 1958 pregnancy of patient S. F. at the third month of pregnancy and in the initial stages of the breast hypertrophy. An effort was made to document as many factors as possible which might be related to steroid metabolism or breast growth and lactation.

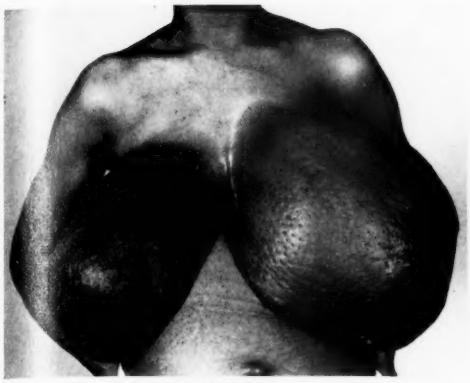

FIG. 4.

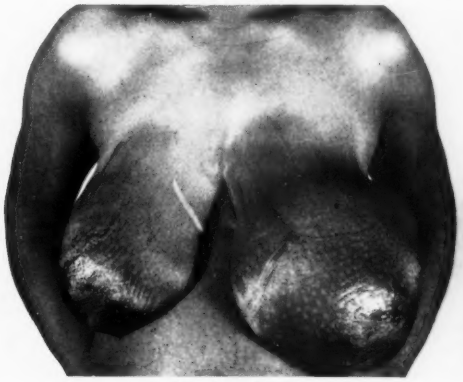

FIG. 5.

FIG. 6.

FIG. 7.

FIG. 4. Patient S. F. showing gigantomastia during seventh month of her third pregnancy. The circumference of the right breast is 63 centimeters and the left breast 80 centimeters.

FIG. 5. Patient S. F. on April 22, 1958. Prior to norethindrone therapy. Patient 3½ months pregnant.

FIG. 6. Patient S. F. July 9, 1958. After 10 weeks of norethindrone therapy breasts show no increase in size but only a change in contour.

FIG. 7. Patient S. F. on September 10, 1958. After 18 weeks of norethindrone therapy breasts still show no increase in size. Patient now 8 months pregnant.

The laboratory findings indicated that there was a depression of all steroid hormone metabolites in the urine and a decrease in the liver function as manifested specifically in inability to conjugate salicylates. These changes may be important factors in the cause of gigantomastia associated with pregnancy. This theory coincides well with the clinical picture in that the difficulty does not arise until the third month or shortly thereafter in pregnancy at which time the steroid load begins to increase with increased placental steroidogenesis; the breast hypertrophy recurs with each pregnancy once the condition is established; in the absence of pregnancy, when there is no steroid overload, the liver function is apparently normal and the breasts are normal in size; the pituitary hormones, somatotrophin and prolactin, said to be associated with breast growth and lactation, are apparently normal. Although it is believed that these 2 patients have demonstrated obvious difficulty in steroid hormone metabolism, it should be

pointed out that pregnant patients with liver damage severe enough to produce jaundice do not show this abnormal breast hypertrophy. It would seem, therefore, that perhaps in addition to the disturbance in steroid metabolism and liver function one must also postulate a target organ sensitivity to account for the gigantomastia. This seems quite reasonable in view of the difference in the actual size of the two breasts observed in patient S. F., as well as the frequently noted clinical curiosity of unilateral gynecomastia.

Various types of hormone therapy for this condition were attempted. Patient T. T. received estrogen during her first pregnancy in an effort to suppress breast hypertrophy. It was obvious that the course of the illness was aggravated by this hormone. The circumference of the chest prior to therapy had been 105 centimeters, and after therapy (7,640 mgm. of stilbestrol in 18 days), the chest circumference actually increased to 107 centimeters and the patient's discomfort was marked. The administration of testosterone propionate in the subsequent pregnancy of T. T., as well as in the first pregnancy complicated by gigantomastia of S. F., certainly did not produce any noticeable improvement. In the 1958 pregnancy of S. F., it was decided to use an orally active progestogen in an effort to ameliorate the gigantomastia. The biopsy report revealed a substantial fibrous tissue hypertrophy which, under some experimental conditions, can be produced by unopposed estrogen stimulation. The pregnanediol assays also indicated that the progesterone production might be low in these patients. A potent progestogen like norethindrone was considered worthy of a therapeutic trial. The improvement of patient S. F.'s condition, as well as the fact that the expected progression of the gigantomastia with pregnancy failed to develop, was most gratifying. The clinical improvement was also manifest in the improved urinary pregnanediol excretion over that seen in the previous pregnancy as well as the apparent improved estrogen excretion although in this instance there was only a single value for comparison.

It is interesting to speculate upon the mechanism of the apparent clinical results. This steroid might have induced an actual shift in steroidogenesis and changed the ratio of estrogen-progesterone production. Or in some fashion it could have improved the steroid conjugation function of the liver, thus decreasing the tissue concentration of all "free" steroids. The progestational drug might have complemented or "neutralized" an estrogen effect on the breast tissue itself. None of these theories seems to satisfy all of the laboratory and clinical findings, and the answer remains to be found in further investigations on subsequent patients.

It is hoped that the successful hormonal management of this patient will encourage others to attempt similar endocrine evaluations and therapy in an effort further to substantiate the rationale and value of such treatment. If norethindrone proves to be as successful in other patients as it was in the latter patient in the present report, it will be of considerable importance as it may obviate not only considerable discomfort but it should put an end to mutilating and unnecessary surgery. It was and perhaps still is common practice to amputate one or both breasts for this essentially benign disturbance.

The hormonal relationships between this entirely benign excessive breast hypertrophy and the neoplastic growth of breast cancer remain to be clarified by endocrine methods and biochemical yardsticks yet to be discovered.

SUMMARY AND CONCLUSIONS

1. Two patients with gigantomastia complicating pregnancy are reported.

2. The incidence, etiology, and pathogenesis of this unusual clinical condition are discussed.

3. A comprehensive clinical and laboratory profile including extensive hormone assays was obtained in 1 of these 2 patients.

4. The data indicate a depression of all steroid hormone metabolites in the urine

and a decreased liver function as measured by the salicylate conjugation test.

5. In addition to a disturbance in steroid metabolism and a decrease in liver function, it must be assumed that gigantomastia also represents an abnormal target organ sensitivity.

6. Conservative treatment with the progestational agent norethindrone (norlutin®) 20 milligrams daily appeared to control the gigantomastia and to arrest its progression during the last half of pregnancy.

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THE IMPORTANCE OF THE VASA VASORUM OF THE AORTA

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By definition the vasa vasorum are the vessels that supply the large arteries and veins with blood. "These nutrient vessels, called the vasa vasorum, arise from a branch of the artery, or from a neighboring vessel at some considerable distance from the point at which they are distributed; they ramify in the loose areolar tissue connecting the artery with its sheath, and are distributed to the external coat, but do not, in man, penetrate the other coats; in some of the larger mammals a few vessels have been traced into the middle coat."

The vasa vasorum as an anatomic entity were known for over 200 years, but references to these vessels are usually vague. The accepted description is that they do exist and are found in the adventitia and in some animals in the muscular layers of the large blood vessels, and that each of the vasa vasorum is accompanied by two vena vasorum which run perpendicular to the long axis of the host vessel. The best reference to this structure was made by Woodruff who did his investigative work on the horse and dog.

Our interest was particularly aroused in these vessels when an attempt was made to explain the failure of suture lines in homologous vascular replacements. Furthermore, it was noted that when vascular clamps with sharp edges caused tracks in the normal aorta these areas ruptured although the suture line fused. Because of these failures we believed that the host vessel segments were devascularized and that homologous vessel grafts were completely devascularized structures in which secondary saccular aneurysms would develop and failure would result.

Stern related the vasa vasorum to arteriosclerotic pathogenesis, while Lowenberg and Shumacker were concerned with these vessels in relationship to vascular repair. Barbareschi as well as Short investigated the vasa vasorum in the larger vessels of the body. McCloskey and Chu developed the work of Stern another step when they investigated the vasa vasorum as an etiologic factor in the development of dissecting aneurysms.

All the major texts of anatomy mention these vessels, and some describe them in the media and adventitia, but as to the actual origin of these blood vessels one finds no description.

When an organ, especially one the size of the aorta, is deprived of its blood supply it must of necessity undergo degeneration. Examination of multiple slides by varied methods of staining failed to demonstrate any of the small microscopic channels that are stated to run from the lumen of the vessel to the subintimal area for regional nourishment.

When it was definitely determined that the vasa vasorum arose from an intercostal or a lumbar artery a method of retrograde perfusion was used. The contrast material was perfused through a large segment of an intercostal artery. With the cannula in the intercostal artery the vasa vasorum were filled with contrast media (Fig. 1). Immediately a flare of dye was seen extending along the long axis of the aorta from a small obvious branch of this intercostal artery. These minute branches of the vasa vasorum apparently do not cross over the aorta where

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FIG. 1. This roentgenogram shows the cannula in the intercostal artery for a retrograde injection study of its branching vasa vasorum. The excess bismuth oxychloride puddled in the lumen of the aorta.

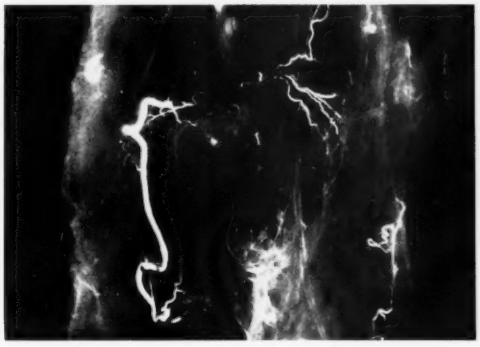

FIG. 2. This roentgenogram shows an unusual pattern. A connection between two intercostal arteries on the same side. Vasa vasorum spring from each intercostal artery.

it is immediately behind the pleura or the peritoneum, as seen in Figure 2. On the other hand, the loose areolar area behind the aorta appears to act like a mesentery, and in this area accessory vessels are found. This is shown in Figure 4. These vessels are of a larger caliber and ramify in all directions.

Segments of the aorta in the region of either an intercostal artery or a lumbar artery were also studied for intramuscular branches. These signet ring segments of aorta showed the same vascular pattern seen previously in our studies of the vascular patterns of the small intestine (2, 3). This is shown in Figure 6. The branches within the media circled the aorta and also ran parallel with the long axis of the vessel supplied by these nourishing branches. Figures 3 and 5 show the vasa vasorum as they leave the intercostal artery. The vasa vasorum do not cross over the so called mesentery but perforate the adventitia to enter the media as shown in Figure 8. Some of the vasa vasorum from one intercostal or lumbar artery cross and anastomose with vasa vasorum from the next intercostal artery either above or below its segment. Figure 8 is a section of the aorta through an intercostal artery. This photograph of a hematoxylin and eosin section shows the intercostal artery and the vasa vasorum in close approximation.

MATERIAL AND METHODS

Numerous human aortas were furnished us by Dr. Robert Haukohl of the Evangelical Deaconess Hospital from available postmortem material. These vessels were washed in cold water, and all of the branches were clamped and tied. Care was taken to tie these branches as far from the parent vessel as possible. A cannula was inserted into the proximal end of the aorta, and a suspension of bismuth oxychloride was injected into the vessel at a pressure of about 120 millimeters of mercury. At this time the vessel was observed for leaks or fluid dissection. All leaks were tied, and if the dissection of the vessel by the bismuth oxychloride was

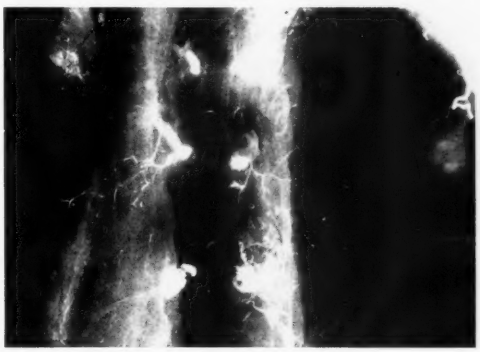

FIG. 3. This roentgenogram shows the prominent intercostal arteries. No anastomosis across the midline. The vasa vasorum are spread out in all directions to supply the host vessel.

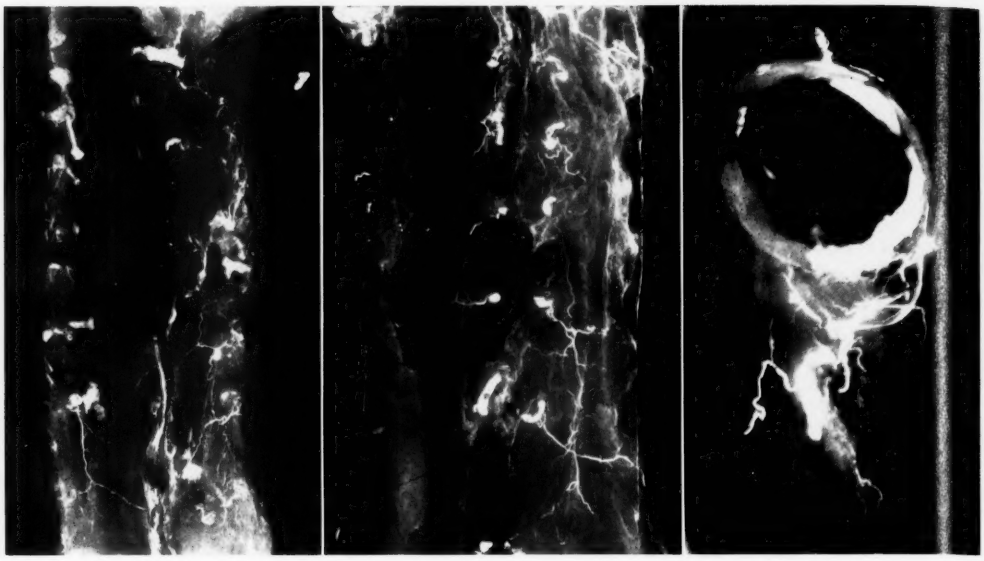

FIG. 4. FIG. 5. FIG. 6.

FIG. 4. When vessels are present in the attached portion of the aorta, "mesentery," the vasa vasorum tend to send branches to anastomose with these vessels. A section of tissue was removed from this specimen in the region of the intercostal artery for homatoxylin and eosin stain.

FIG. 5. This roentgenogram shows the parallel arrangement of the intercostal arteries with minute vasa vasorum coming from the lateral aspect of each of these vessels. The vasa vasorum do not cross over the midline of the host vessel.

FIG. 6. This roentgenogram shows a transverse section of the intact aorta at the level of an intercostal artery. The course of the vasa vasorum can be readily seen. The plaques within the lumen of the aorta show the extensive arteriosclerosis with the obliteration of the vasa vasorum in this region.

small the leak was found and controlled; if, however, the dissection progressed for a distance the specimen was discarded. The injected specimen was then placed in formalin for fixation.

After fixing, the vessel was cut open along its peritoneal or pleural covered surface and placed on an x-ray plate and exposed to the x-rays by using 50 kilovolts, 7 milliamperes, 15 inch distance for 1 second. Some of the specimens were injected with dilute India ink for contrast and microscopic studies. Horizontal or signet ring sections were then made.

These specimens were dehydrated in absolute alcohol and then placed in methyl salicylate for clearing. The specimens were examined under the high power (36×) of the compound dissecting microscope for the presence of the intercostal vessels and the branching of the vasa vasorum. This method was also used on sections taken in the lumbar region where the lumbar arteries were examined for the origin of the vasa vasorum. Hematoxylin and eosin stains of sections cut at 10 microns were examined for the smallest possible vessels supplying these larger vessels.

To evaluate this study of inert tissue, live dogs were also injected while under nembutal anesthesia. In some of these experiments the animals were first perfused with 5 per cent procaine intravenously to aid in the suppression of vascular spasm in the belief that this might enhance the injection of the smallest vessels. No other vessels, however, were observed nor was the injection of greater magnitude.

FIG. 7.

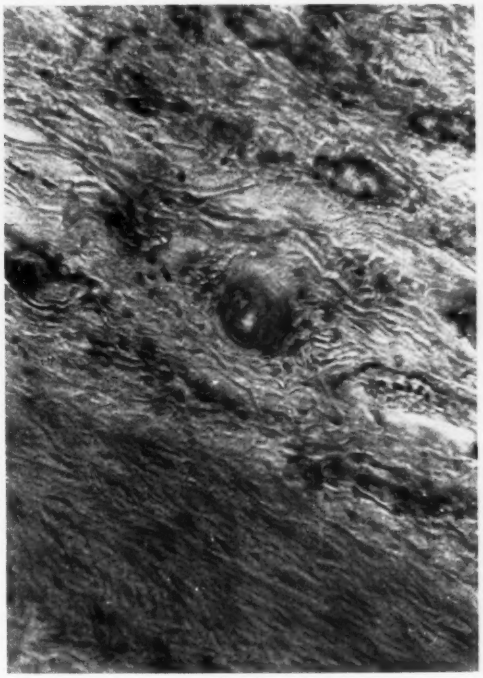

FIG. 8.

FIG. 7. A hematoxylin and eosin study at low power showing the intercostal artery as well as the lumina of the vasa vasorum at the same level.

FIG. 8. A hematoxylin and eosin study of the vasa vasorum in the media of the aorta.

DISCUSSION

"So little but so mighty" might aptly describe the vasa vasorum. These small vessels arise from a major branch of the host vessel to return to the parent vessels for nourishment of this vessel. In the case of the aorta, the vasa vasorum arose from an intercostal artery in the chest or a lumbar branch in the abdomen. Our investigation was limited to the aorta. The importance of the vasa vasorum assumes greater proportions as their destruction in the transfer of a homologous vessel graft would explain the formation of secondary saccular aneurysms in this transplant and also show why homologous grafts are poor replacement material of a host aneurysm. The obstruction of these small vessels, as in arteriosclerosis by a calcific plaque or as in endarteritis leading to medial necrosis, would readily explain the blowout and aneurysm formation in these anatomic entities.

SUMMARY

In an attempt to explain the failure of homologous vessel grafts we investigated the vasa vasorum. Textbook references mention these vessels but do not state their origin. In human beings, it has been stated that the vasa vasorum do not enter the media of the vessel which they supply. We found that the vasa vasorum are present in the media. However, the microscopic canals that supposedly run from the lumen of the aorta to the subintimal area could not be demonstrated. From our work we believe that a resection of a segment of the aorta should not involve its immediate intercostal artery in the chest or the lumbar artery in the abdomen. The vasa vasorum of the aorta arise

from the intercostal arteries as well as from the lumbar arteries and not directly from the lumen of the aorta. These vessels are of extreme importance in the surgery of major vessels, and their absence is the prime cause of homologous vessel transplant failures.

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HUMAN CARTILAGE GRAFTS STORED IN MERTHIOLATE

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FOR MANY YEARS, in the field of reconstructive surgery, a supporting material has been sought for the correction of contour defects. Certain criteria have been postulated as being necessary and desirable. The general plan of study was to determine whether viability is essential to the success of a cartilage homograft. To this end, various storage media were selected to maintain the viability of cartilage or to kill it. Some of the general characteristics of fresh living human costal cartilage were reported previously (1). The scope of the present article is limited to the study of cartilage stored in merthiolate-saline solution and later transplanted into human volunteers.

METHODS

The method of preparation of the cartilage has already been described (1). The prepared cartilage was placed in sterile bottles containing 1:4,000 merthiolate-saline, capped, and refrigerated at 3 to 5 degrees C. Merthiolate-saline was selected to kill the cartilage in such a manner as to least disturb the tissue. Merthiolate-saline solution in even lesser concentrations is toxic to tissues. Rapid penetration of the merthiolate solution into the cartilage within 19 hours was demonstrated by the presence of mercury in the center of the tissue. One inch blocks of cartilage which had been stored in merthiolate-saline solution for varying periods of time were transplanted subcutaneously into the abdominal wall of human volunteers. The implants remained in the host for a predetermined time and were then removed for examination. Fibrous tissue invasion in transplanted cartilage was measured in the following manner: a histologic section of cartilage was placed in a photographic enlarger and the image projected at a magnification of ×13.25. The periphery of the image and the centrally placed islets of invading fibrous tissue were traced and their area determined by a planimeter. Only the central islands of invasion were measured since the peripheral areas could not be distinguished from irregularities in contour produced by the preparation of the tissue. Areas of invasion were expressed as the per cent of cross sectional area of the cartilage block.

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RESULTS OF CARTILAGE STORED IN MERTHIOLATE

Supravital stains. Sixty-nine specimens from 25 cadavers were examined microscopically, revealing rapid death of the cells with no viability at the end of 2 days of storage. Fifty-one specimens taken from the same cartilage blocks were stored under identical conditions, except that the merthiolate-saline solution was omitted as a storage medium. These control specimens were examined simultaneously with the merthiolate-stored specimens and exhibited 95 to 98 per cent viability at the end of the same 2 day storage period. Buffer ranges from *p*H 6.6 to 6.8, 6.8 to 7.0, and 7.0 to 7.2 were utilized in staining to exclude the possibility of *p*H change reducing the dye to its colorless leucobase.

Metabolic studies. One hundred and fifty-six determinations were made on cartilage from 26 cadavers. The anaerobic glycolysis ($Q_G^{N_2}$) decreased to zero within 2 days, and thereafter tended to remain at this level (Fig. 1).

Histologic studies. Twelve pieces of cartilage, stored for periods varying from 7 to 216 days,

TABLE I.—SALT AND WATER SHIFTS IN HUMAN COSTAL CARTILAGE AFTER STORAGE IN MERTHIOLATE SOLUTION

Condition of cartilage	*No. of determinations*	*Days stored*	*Days transplanted*	*Na mEq./kgm.*	*K mEq./kgm.*	*Per cent H_2O*	*I Na* mEq./L.*	*I K† mEq./L.*
Fresh	64	..	....	172.46	20.3	60.8	.....	.....
Stored	56	28	....	239.57	5.0	61.1	153.00	0.0
Stored and transplanted	8	19	531	216.75	7.53	59.5	.....	.....

*I Na = Sodium concentration of the storage medium.
†I K = Potassium concentration of the storage medium.

TABLE II.—CALCULATED VALUES OF SALT AND WATER SHIFTS WITHIN COSTAL CARTILAGE

Condition of cartilage	*Days stored*	*Days transplanted*	*Int.* c.c./kgm.*	*Ext.† c.c./kgm.*	*△ Na mEq./kgm.*	*△ K mEq./kgm.*	*△ Int.‡ c.c./kgm.*	*△ Ext.‡ c.c./kgm.*
Fresh	..	....	145.00	463.00	.....	.....	.....	.....
Stored	28	....	37.50	575.30	+67.11	−15.30	−109.3	+112.3
Stored and transplanted	19	531	53.60	541.40	−22.82	+2.53	+7.9	−34.1

*Int. = intracellular water volume.
†Ext. = extracellular water volume.
‡△ = change of quantity measured.

TABLE III.—TRANSPLANTED CARTILAGE (MERTHIOLATE-STORED)*

Age in Years		*Days*		N_2 *Q G*	*Per cent normal*	*Per cent pyknotic*	*Per cent karyolytic*	*Per cent "dropped-out"*	*Total area†*	*Central fibrous tissue†*
Donor	*Recipient*	*Stored*	*Transplanted*							
39	29	26	134	+0.057	9	11	67	13	151.22	.3016
6	48	28	163	+0.048	31.5	7.5	31.5	29.5	182.21	2.010
6	24	18	172	+0.184	0	0	82.5	17.5	44.35	.0912
6	42	7	174	+0.142	0	1	90	9	54.44	.1390
39	23	34	447	+0.004	0	8	84	8	157.61	.1866
24	20	18	453	+0.057	0	3	76	21	114.38	.1000
6	16	18	471	+0.077	0	0	95	5	73.98	.1270
43	40	14	791	+0.064	0	3	85	12	176.84	.4200
6	40	12	939	+0.011	0	9	78	13	95.81	0
6	3	26	1039	+0.047	0	2	55	43	58.29	0
36	9	6	1059	+0.062	6	6	81.5	6.5	89.12	6.855
					Average values					
20	29	19	531	+0.069	4.2	4.6	75.1	16.1	108.93	.9300

*=None of the cartilage was viable by supravital stains.
†=cm.²
Per cent total central fibrous tissue .85.

were examined histologically. All sections showed some evidence of necrosis and, in a few instances, bacterial growth. The architecture of the tissue in general was well preserved.

Electrolyte and water exchange. Fifty-six analyses each of sodium, potassium, and water content were made on stored cartilage from 18 cadavers. As compared with control values obtained in analyses of fresh cartilage, in cartilage stored in merthiolate-saline solution for an average of 28 days the sodium content increased by 39 per cent, the potassium content was reduced by 75 per cent, while there was a negligible gain of water content (Table I). Values derived by methods described previously (1) revealed the intracellular water volume to be decreased by 75 per cent and the extracellular water volume to be increased by 25 per cent (Table II).

RESULTS OF TRANSPLANTED CARTILAGE PREVIOUSLY STORED IN MERTHIOLATE

Supravital stains. Fourteen pieces of merthiolate-stored cartilage, which had been transplanted into 11 patients for periods of time varying from 134 to 1,059 days, were examined for viability by supravital staining. As an average, 4 sections of each specimen were taken, at spaced intervals, through the tissue block. None of the cells appeared viable (Table III).

Metabolic studies. Thirty-seven determinations were made on merthiolate-stored cartilage which had been transplanted into 11 pa-

tients for 134 to 1,059 days. The mean anaerobic glycolysis was +0.069 (Table III). This value is approximately 30 per cent above that for fresh cartilage.

Histologic studies. Histologic examinations were made on 23 pieces of merthiolate-stored cartilage which had been transplanted into 11 human volunteers for periods of 134 to 1,059 days. There was an average of 4.2 per cent normal cells, 4.6 per cent pyknotic, 75.1 per cent karyolytic, and 16.1 per cent "dropped-out" (Table III). Fibrous tissue invasion, comprising central areas only, averaged 0.85 per cent. Infiltration by lymphocytes and macrophages was minimal.

Electrolyte and water exchange. Eight analyses each of sodium, potassium, and water content were made on merthiolate-stored cartilage which had been transplanted into 4 human volunteers for 791 to 1,059 days (Table I). As compared with nontransplanted cartilage stored in merthiolate, the sodium content of transplanted cartilage decreased 10 per cent, while the potassium and water exchanges were slight (Table II).

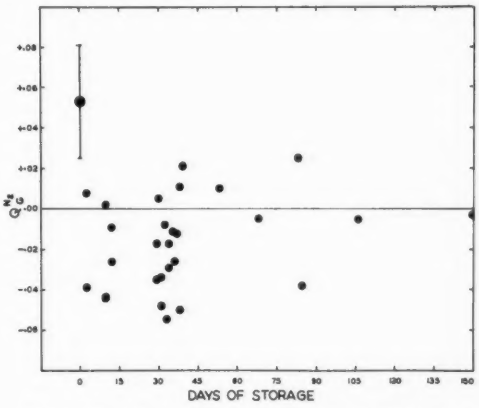

FIG. 1. The effect of merthiolate-saline (1:4000) on the anaerobic glycolysis of adult human costal cartilage. The bar for fresh cartilage represents two standard deviations.

DISCUSSION

Cartilage stored in merthiolate became nonviable within a few days. Since each of the methods of study may measure a different facet of viability, their correlation on the exact time of death is not to be expected. In addition, the wide range of end-points within each of these methods further decreases the exactness of this determination. For example, the method of preparing the tissue for histologic examination produces instantaneous cellular death. Yet, these killed cells are interpreted as appearing normal, if there is no evidence of degenerative changes. Further, it is possible that all of the cells in the merthiolate-stored group which appear histologically normal may be nonviable, since the cytoarchitecture may be preserved by the storage medium. Despite these variations, there is little doubt that all of the cells of the cartilage are killed within a short time after storage in this medium. The electrolyte and water studies generally support the findings of rapid death of cartilage cells exposed to merthiolate-saline solution (Table I). The loss of potassium may be explained by a decrease in the number of viable chondrocytes during storage (Table I), since practically all of the potassium exists intracellularly. Calculations of the intracellular water volume based upon intracellular potassium content, results in a reduction from a normal of 145 cubic centimeters per kilogram to 37.5 cubic centimeters per kilogram of wet cartilage (Table II). The extracellular water volume, total water less intracellular water volume, was increased by two events: first, as a consequence of the decrease of the intracellular water volume, and second, by a slight increase in total water (Table II). The gain of sodium by cartilage during storage in merthiolate-saline (Table I) is due to at least 3 distinct mechanisms. First, the chondrocytes disintegrate during storage, their intracellular water volume becoming a part of the extracellular water volume. The intracellular water volume does not contain sodium, while extracellular water contains about 144 milliequivalents of diffusible sodium per liter—the extracellular diffusible sodium being in equilibrium with tissue fluid. Thus, a conversion of approximately

109 cubic centimeters of intracellular water volume per kilogram of cartilage into the extracellular water phase would account for a gain of about 16 milliequivalents of sodium per kilogram of cartilage tissue. The second mechanism of sodium gain is due to the slight shift of storage medium water into the cartilage (Table I), and this accounts for about 0.5 milliequivalents of sodium per kilogram of cartilage. The third mechanism appears to be an actual sodium binding by the cartilage matrix. The first two mechanisms account for only 16.5 milliequivalents of sodium per kilogram gained, while the cartilage actually gained a total of 67.0 milliequivalents of sodium per kilogram of tissue. This leaves 50.6 milliequivalents of sodium per kilogram of cartilage presumably bound by the cartilage matrix.

These results of sodium, potassium, and water exchange substantiate the early death of the cartilage cells stored in merthiolate-saline solution as determined by supravital dye studies, histologic examinations, and metabolic studies. This is of special interest since merthiolate-saline is one of the most popular storage media for cartilage in clinical use.

All of the transplanted cartilage was stored in merthiolate-saline solution (for an average of 19 days; a minimum of 6 days) prior to transplantation. Our data indicate this cartilage to be nonviable as a result of storage alone. Therefore, it was to be expected that the transplanted cartilage would show no evidence of viability. In general, the results of all our studies supported this view.

The mean anaerobic glycolysis of cartilage which had been transplanted for long periods of time after previous storage for approximately 19 days in merthiolate-saline is higher than that for fresh cartilage (Table III). Since prior storage has been demonstrated to kill cartilage, the elevated anaerobic glycolysis after transplantation cannot be explained in terms of chondrocyte viability. However, it can be the result of invasion by host tissue. Since the invading host tissue should have a relatively high anaerobic glycolysis, being an active tissue, the presence of even small amounts of such tissue would endow the dead transplanted cartilage with a detectable anaerobic glycolysis, in some cases even higher than that of fresh cartilage.

The amount of central fibrous tissue invasion represents 0.76 per cent of the total cross sectional area of transplanted cartilage. This figure is derived by subtracting the amount of centrally placed connective tissue and blood vessels found in fresh cartilage (0.093 per cent of total cross sectional area) from the total amount of fibrous tissue and blood vessels found in merthiolate-stored transplanted cartilage (0.85 per cent).

The gain of potassium during transplantation (Table II, col. 6) is probably due to the difference of the potassium concentration between the interstitial fluid of the host and that of the storage medium. When stored cartilage is transplanted, the potassium of the host will reach an equilibrium with the total water of the transplanted cartilage (Table I), accounting for a gain of 2.5 milliequivalents of potassium per kilogram of cartilage tissue. This agrees well with the observed gain of potassium (Table II).

Of the sodium lost by the transplanted cartilage, only 2.3 milliequivalents can be explained by the decrease in total water of the cartilage. The remainder of the sodium which was lost (20.5 mEq./kgm.) came presumably from the bound fraction. Whether this indicates a loss of binding material from the cartilage matrix or just a replacement of the bound sodium by another cation, possibly calcium, is not known.

The combined effects of storage and transplantation on the electrolyte pattern of human cartilage may be summarized as follows: There occurred an over-all net gain of 44.3 milliequivalents of sodium per kilogram and an over-all net loss of 12.8 milliequivalents of potassium per kilogram of cartilage tissue. The loss of potassium was due to the death of the chondrocytes in the merthiolate-saline storage medium, with a consequent loss of intracellular water volume. While the cartilage gained large amounts of

sodium when placed in the storage medium, after transplantation this gain tended to be lost, although the level remained above that of fresh cartilage.

SUMMARY

Cartilage was killed rapidly by storage in merthiolate-saline solution. This was established by supravital stains, metabolic studies, histologic examinations, and electrolyte water assays. During the period of storage, there was a pronounced loss of potassium and gain of sodium. After transplantation, the nonviability of the cartilage was substantiated by all methods of examination, save anaerobic glycolysis determinations. Since all of this cartilage was dead at the time of transplantation, the elevated anaerobic glycolysis indicated the presence of cells of a higher rate, probably invasive host tissue.

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EDITORIALS

CANCER IMMUNITY

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RECENT technical summaries of cancer immunity, emphasizing either basic research or clinical studies, are available to surgeons willing to accept the challenge of a new vocabulary and the alphabetic intricacies of inbred mice. Actually, there have been few alterations in the immunologic principles first enunciated at the turn of the century, but later studies have defined more accurately the limitations of these principles as they pertain to the cancer problem.

There is little doubt that host resistance factors are intimately associated with the development and progress of human malignant disease. Unfortunately, most of the evidence is indirect, and the mechanisms involved are poorly understood. The existence of such factors is suggested by these observations: (1) spontaneous regression of established tumors; (2) prolonged survival of patients after incomplete removal of their cancer; (3) the sudden appearance of widespread metastases many years after apparently successful treatment of the primary lesion; (4) regression of metastases after treatment of the primary tumor; (5) evidence that thousands and millions of tumor cells are exfoliated into the blood stream and lymphatics without the development of a comparable number of metastases; (6) histologic evidence of histiocytic and lymphocytic (and plasmocytic) responses in the vicinity of some tumors and in the regional lymph nodes; (7) the appearance of antitumor antibodies in the serum of a few patients; (8) the development of hypersensitivity by certain patients to some components of their tumors; (9) demonstrable changes in immunologic responsiveness paralleling exacerbations and remissions of certain malignant diseases; (10) evidence suggesting enhancement of tumor growth by cortisone and certain toxic carcinostatic drugs; (11) the low incidence of successful autotransplants of tumor tissue in cancer patients.

Much of the early enthusiasm for immunologic control of cancer stemmed from laboratory experiments employing transplantable tumors in animals. Unfortunately, many of these studies used tumors genetically foreign to the animals, and it became apparent that much of the "cancer immunity" was merely an expression of genetic differences between the transplantable tumors and their hosts. In effect, tumors were being used to study homograft responses in the animals.

Subsequently, a number of workers made careful studies of the immunologic relationships of transplantable tumors to the inbred hosts of origin. Existence of specific tumor antigens in a number of these tumors was established, and cytotoxic antibodies were prepared which provided effective passive immunity to subsequent challenge with tumor cells. Nevertheless, despite the development of highly inbred strains of mice and the lack of demonstrable mutations in the tumors, it is difficult to be sure that subtle, undetectable genetic differences may not account for some of the favorable results.

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Further evidence that resistance of the host may influence the growth of transplantable tumors is found in studies which correlate depression of host immunologic responses with enhancement of tumor growth. Abrogation of host defenses and stimulation of tumor growth have been accomplished for a variety of tumors by such methods as: (1) irradiation of the host; (2) pretreatment of the host with cortisone; (3) stress, infection, surgery, toxic compounds, and exhaustion; (4) suppression of immunologic responses by injecting the future host with treated whole cells or certain cell fractions while still in the embryonic stage (immunologic tolerance); (5) blockade of the reticuloendothelial system with colloidal particles.

Both experimental and clinical investigations have shown that immunologic differences may exist between a spontaneous tumor and its host. This is not surprising, since one might expect some such changes to occur during the complex process of malignant transformation. The cancer cell is obviously different from its neighboring normal cells and probably must survive and multiply in an initially unfavorable environment. The important point is whether or not these antigenic differences can be magnified and used for diagnostic and therapeutic purposes.

The thesis that mutations occur frequently during the entire life of living organisms, and that only a very small number of the resulting abnormal cells survive as malignant cells, was first proposed almost 60 years ago by Boveri. Briefly, abnormal cells may be formed by injury to the genetic apparatus, including duplication of one or more chromosomes, deletion of chromosomes or genetic material, dissociation of normally related genetic units, and perhaps deletion of nongenetic substances, or injury to them, thus preventing expression of the normal genetic pattern.

Abnormal cells in the human being may be produced by a wide variety of chemical and physical agents (x-rays, actinic rays, and chemical carcinogens), abnormal nutritional states, and possibly also by infective particles such as viruses. Cell mutations caused by viruses may differ from those resulting from other agents because these mutations are apparently caused by addition or substitution of foreign genetic material in the recipient cell (transduction), rather than by duplication or deletion of genetic fragments of the target cell. The types of cell injury which predispose the cell to the acceptance of foreign genetic substance are largely unknown. They are, however, being thoroughly studied by means of phage-bacterial systems. This concept is important to a discussion of cancer immunity since the separation, identification, and mechanisms of action of genetic material or even of nucleic acid fragments may soon be possible.

There are doubtless many other causes of malignant cell transformation which are not as yet recognized. Fortunately, the great majority of these abnormal cells probably fail to survive because of such inherent factors as an imperfect nutritional apparatus, faulty mitotic apparatus, or the absence of critical enzyme systems. The few abnormal cells which do survive may become precursors of fatal cancer. These cells are probably subjected to further attack by local and systemic host defenses, including true immunologic defenses, and only the final surviving cells, through adaptation to a hostile environment, are capable of unrestrained malignant growth.

Perhaps one is justified in suggesting that mature human cancers range from those tumors which survive only because they are nearly identical with adjacent normal cells, to those which differ genetically but have a growth potential so great that autonomy is established even despite immunologic differences. Probably only the latter sort of tumors could be expected to be destroyed with vaccines. This thesis is supported by some experimental data which indicate a range in initial antigenicity of tumors. Foley, and later Prehn and Main, showed that tumors induced with carcinogens seem to have more mutational changes than "spontaneous" tumors have and exhibit wider immunologic

variations with respect to the host. A few spontaneous animal and human tumors have been shown to be weakly antigenic to the host. It is not yet known whether these antigens are specific to the healthy tumor cells, or arise from altered proteins of damaged cells, or from stromal elements.

Limited studies indicate that certain patients may develop hypersensitivity either to their tumors or to products of their tumors. Unfortunately, such responses cannot be correlated with increased host resistance in these patients. Generally, there is little doubt that immunologic responses to human tumors do occur. These probably will be found more commonly in the future as new immunochemical methods are developed. Of great interest are the nonmalignant autoimmune mechanisms in man, such as chronic thyroiditis and certain hemolytic anemias.

The chances of developing an effective tumor antiserum for complete eradication of established solid tumors appear remote at present, but the possibility of enhancing the cellular responses of the host to his tumor seems promising. Graham and Graham are now evaluating this approach by using tumor autovaccines. One hopes that the tissue culture of large amounts of tumor cells may aid in similar future projects by supplying a source of altered autogenous cells which might provoke stronger cytotoxic reactions.

Attempts also have been made to transfer homologous cells capable of producing tumor antibodies to the tumor-bearing host. These homografted reticuloendothelial cells may indeed function against the tumor cells, but they also function against the normal host cells. Also, unless the recipient's own immunologic responses are markedly depressed, the transplanted cells are soon rejected.

Development of an effective preventive immunization against cancer involves a myriad of complex problems. Such a vaccine should be polyvalent both as to origin and kind of malignancy. It must be effective despite the enormous diversity of human genetic backgrounds. While it seems plausible that the cancer cell would probably be most vulnerable to the effects of such a vaccine at the moment of its inception, the changes from normalcy to malignancy may be so subtle that they would be accepted by the surrounding host cells without provoking the defensive mechanisms. Furthermore, established tumors are not made up of a single kind of cell. The cells of most tumors have wide variations in such gross characteristics as chromosome number, growth rate, and susceptibility to therapeutic agents. Thus the search for a broad-spectrum vaccine which could be directed against even a single tumor would be an arduous one indeed.

On the other hand, the isolation of infective tumor-inducing viruses from "spontaneous" malignant lesions in mice, as well as from those induced by carcinogens and x-rays, may alter present concepts. The polyoma virus, for example, can induce not just one type of tumor, but some 6 to 8 different types, all in the same mouse. In addition, it is capable of crossing species barriers and producing tumors in hamsters and rats.

Protection against tumor induction with this virus has already been accomplished by immunization against the agent. Likewise, protection against a number of other viruses that induce tumors in animals has been effected by appropriate immunization procedures. Reports have now appeared concerning the isolation of similar agents from human tumors which either induce or accelerate the development of tumors in experimental animals. The significance of these observations to any projected search for a biochemical difference between normal and malignant cells is obvious, and the immunologic implications are manifold.

The role of host defense mechanisms, other than orthodox immune responses, cannot be adequately discussed here. Nevertheless, the meanings of the subtle physicochemical interactions which control production of genetic materials and utilization of "synthetic" normal genetic fragments for the repair of abnormal cells are representative of the exciting, new challenges in this particular area of research.

PHYSICIANS' RESPONSIBILITY IN BLOOD TRANSFUSION

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THE INCREASED USE of blood transfusion in recent years has had the strange effect that most clinicians know less rather than more about the subject, simply because its growing complexity has thrust it into the province of specialized knowledge. The physician who orders blood for a patient cannot be expected to be well versed in all aspects of this knowledge—for example, the immunohematologic—but, since he orders the transfusion and carries the responsibility for the results, it is essential that he keep apace with the problems rather than shy away from them. Pathologists and blood bank directors are seldom clinicians closely associated with the patient.

Blood transfusion is a risk which can be calculated only with knowledge of the dangers. For the best results, the clinician must be aware of the laboratory problems and have a clear concept of the harmful effects as well as the objectives. Important among dangers are reactions due to incompatibility (ABO, Rh, and others). Since these are caused by laboratory error and confusion of samples and units of blood, the doctor should be certain that the laboratory is well supervised and that minimal standards are observed within his institution. Survey is available through the American Association of Blood Banks. When there is urgent need for transfusion it is essential to know when to disregard Rh and other secondary blood group considerations. One should be able to ask and interpret the significance of such questions as whether the patient can ever have a child, whether there has been prior sensitization, and whether interval transfusion is expected. More education is needed on these and related subjects at the practitioners' level in local medical society and hospital staff meetings.

There is a variety of other risks to be considered. Every transfusion is a potential source of transmission of disease. About 1 in every 300 units of blood transmits viral hepatitis, despite the most careful donor selection. Two to 4 per cent of all units of stored blood contain bacteria. Most do not grow at storage temperatures and are nonpathogenic but some, such as the coli-aerogenes group, do grow and the effects are almost always lethal. Overload reactions may be due to overzealous transfusion and, as hypotension develops, the error is sometimes compounded. Under anesthesia these are difficult to recognize. They occur most often, however, with rapid transfusion of even small amounts, 1 or 2 units, in patients with myocardial weakness or severe chronic anemia with normovolemia, such as is present in chronic leukemia and in many gynecologic and cancer patients being prepared for surgery. Plasma transfusion reactions and those due to leuco-agglutinins ("buffy-coat" reactions) and to allergies are also harmful.

In some instances, the dangers of whole blood transfusion may be mitigated and the objectives achieved by substitutions of selected portions of blood. Examples are the use of packed red cells for anemia with normovolemia to avoid circulatory overload, of washed red cells if "buffy-coat" reactions develop, and of pooled plasma stored at 32 degrees C. for 6 months for support of the circulation in emergencies to avoid opportunities for incompatibility, iso-immunization, and viral hepatitis.

A large share of all types of serious reactions would be eliminated and blood would be saved for those who need it simply by stopping the prevalent practice of transfusion in needless circumstances. This is encouraged by ease of procurement from the blood bank and is usually that of a single

pint for poorly defined indications. An analysis made in Cincinnati showed that patients received an average of 2.4 units and that of the 18,000 units issued yearly by the University of Cincinnati Blood Transfusion Service about 5,000 are given to patients who receive only a single unit during the course of their illness.

It is our firm conviction that far too many patients are being given single pint transfusions. These are justified in hemorrhage when the rate and duration cannot be anticipated, as, for example, in certain injuries, gastrointestinal bleeding, and operations such as radical mastectomy. Unfortunately, most are given for such things as minimal to moderate blood loss during surgery of lesser magnitude, transient hypotension due to syncope and various anesthetic agents, false blood pressure readings due to a loose tourniquet cuff, and postoperative hemoglobin determinations of 8, 9, or 10 grams. These situations are best met with simpler measures, such as Trendelenburg posture, peripheral vasoconstrictors, and the use of ferrous sulfate. Each year millions of blood donors lose a pint of blood in from 6 to 10 minutes. Is this an indication for transfusion? Many have reactions accompanied by pallor, sweating, cold extremities, and transient hypotension without requiring transfusion.

WHAT'S NEW IN SURGERY

INTRODUCTION

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WITH THE PASSAGE OF TIME, the annual Forum on Fundamental Surgical Problems has grown both in volume and in the quality of the contributions reported. Some years ago the Forum Committee thought it might be worth while to institute on the final day of the Clinical Congress a "What's New" program. A number of individuals were asked to attempt to digest the vast amount of material presented during the preceding days and to give a concise summary of what they considered to be new and important in the particular fields assigned to them.

From the first, it was suggested that the speakers include, if they so desired, new knowledge presented at other sessions during the Clinical Congress or, indeed, material recently reported at other surgical meetings. Of necessity, such brief reports could not include reference to all that was considered new and valuable, and much that might have been a part of longer presentations had to be excluded. In spite of the enormity of the task and the complete lack of time for deliberate preparation, it soon became evident that these summaries were excellent beyond even the original expectations and that they fulfilled a real need.

The "What's New" presentations were generally so well received that the advisability of their publication as a "bird's eye view" of current progress soon became evident. It is a happy circumstance that arrangements have been made for their publication as a new, separate feature of SURGERY, GYNECOLOGY & OBSTETRICS. I have no doubt that the prompt appearance of these manuscripts, submitted within an editorial deadline and published 4 months after the Clinical Congress, will prove both informative and stimulating.

PLASTIC SURGERY

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THE PLASTIC SURGEON, heir to one of the oldest of the surgical specialties, continues to be concerned with the wound. There is a constant need to reiterate the importance of the arduous, day by day care of raw surfaces and the desirability of early closure by suturing, grafting, or the use of local flaps. No magic short cut or topical agent can replace the faithful removal of soiled dressings, the careful application of fresh dressings to avoid unfilled pockets of unabsorbed exudate in which bacteria will thrive, the removal of unwanted debris, the encouraging of local tissue resistance by aiding the wound to remain as dry as possible, and the protection of the wound from contamination.

Seldom is the granulating wound completely sterilized, but a quantitative decrease in the number of the bacteria inhabiting the raw surface is a valid index of its improved state. The *p*H of the granulating surface is another objective measure of the condition of the wound. The percentage take of skin grafts has been correlated with the *p*H of the wound at the time of grafting. The healthiest granulation tissue usually has a

*p*H 7.4 or above. This direct clinical test may be a helpful method of evaluating the wound, but perhaps the best method of all is inspection of the surface itself. It should be smooth, firm, bright red in color, with minimal exudate, and occasionally showing a marginal spread of epithelium.

Since a granulating surface cannot be sterilized, it occurred to Eade, Bass, Lewis, and Blocker that a study of the fate of bacteria beneath the skin graft would be informative. Measured, small quantities of Gey's solution were injected beneath skin grafts, allowed to remain beneath the graft in a limited area controlled by a ring held firmly against the surface, and then reaspirated. This solution was then studied for its bacterial content and, in later studies, for its content of white cells. These authors reported an abrupt fall in the number of bacteria recovered from beneath the graft within a matter of hours after it had been applied. The leucocyte counts, on the other hand, showed a biphasic fluctuation with sharp increases at 2 and at 8 hours after grafting.

Sokolic, Farpour, and Ulin have demonstrated the same beneficial decrease in the number of wound bacteria using heterografts of stored fetal calf skin. These grafts were not vascularized, produced neither antibody nor second-set reactions, and were rejected after 5 to 13 days with a typical foreign body reaction. In 4 patients, heterografts were used to cover the skin defects caused by the primary excision of a burn. The heterografts were removed at 5 to 6 days and replaced by autografts which "took" completely. It appears that a stored heterograft is useful as a biologic dressing and that it does not alter the later acceptability of an autograft.

Pappas and Hyatt have continued the important search for an ideal biologic dressing suitable for covering extensive raw surfaces in the animal and man. In their most recent study regenerated collagen film, preferably heat-sterilized, was applied directly to the dissected surface. These experiments, carried out on mice, demonstrated the superiority of collagen film over that of skin homograft. The former remained in place for an average of 14 days; the latter averaged only 8 to 9 days.

Bell, Haynes, Hume, and Egdahl reported upon the value of fetal skin used as homografts in the dog and in man. In the dog, they found an inverse relationship between the age of the fetal graft and the duration of survival. No permanent survival occurred. The expected prolonged survival was observed in the burned patient using a control adult homograft, but an even longer survival was noted with a fetal homograft of skin.

Wound contraction has been studied by Grillo, Watts, and Gross. After creating a standard wound in the guinea pig and allowing normal contraction to proceed for periods up to 30 days, various parts of the wound were excised. Distraction of the contracting wound occurred only when the bordering skin and wound margins were excised. This did not occur, however, when the central granulations were removed. They concluded that there is a marginal or "picture frame" localization of the contraction mechanism.

For many years, there has been a clinical impression that cooling lessens the chance of necrosis in transplanted skin flaps if impairment of circulation exists. Ice bags have been applied empirically to endangered skin flaps, and skin grafts have been left exposed to the air, but now a carefully controlled study on the effects of localized hypothermia on pedicle flap tissue has been reported by Kiehn and Des Prez. These investigators designed and constructed a cooling device by which a constant temperature can be maintained in a column of air over a skin surface. A flap prepared on the rabbit's back with borderline blood supply was used in this study. It was noted, consistently, that necrosis began to develop at about 2½ days. When the air column over the end of the flap was cooled to a temperature of between 0 and 5 degrees C., however, the development of necrosis was delayed until 3½ days. At an intermediate temperature of 20 degrees C., necrosis did not occur and there was complete survival of all flaps. This optimal cooling at 20 degrees C. apparently protects the flap from spontaneous necrosis and encourages the establishment of normal arterial and venous flow through the pedicle.

These are but a few of the studies on the wound reported in recent years. Of an even more fundamental nature have been those in which chemical and histochemical methods have been used in following the sequences in the healing wound. Included among these are the studies by Dunphy and Udupa. These investigators implanted ivalon sponge and studied the tissue substances absorbed in the sponge during

the several phases of healing. It was possible to alter the production of mucopolysaccharides which are precursors of collagen, by a variety of deficiencies, physical agents, and additional trauma. In another study, Peacock and Petty attempted to bypass the hydroxylation of proline, which is retarded in protein-depleted rats by adding hydroxyproline to their diets. A large intake of hydroxyproline slowed collagen formation and significantly reduced the strength of the wound. In still another study, several precursors of collagen were added locally to the healing wound. The local insertion of acetic acid reconstituted collagen in the wound hastened recovery of the tensile strength. Mature collagen, on the other hand, acted as a foreign body and delayed recovery of tensile strength.

Finally, Gimble, Veazey and Kapetansky reported that when experimental burn blisters in man, 1 centimeter in diameter, were emptied of their serum and filled with royal jelly daily, epithelialization was accelerated 25 per cent. Royal jelly is the substance fed by the worker bees to the queen and probably contains an extraordinary variety of endocrine and nutritious substances. Further work is in progress to determine which of these constituents is responsible.

Tissue homotransplantation continues to be a stimulating topic for discussion by the plastic surgeon, the endocrinologist, and others. The development of synthetic fabrics has divorced the vascular surgeon from this group. However, differentiation must be made between the homostatic transplant—blood vessels, bone, cartilage—which serves merely as a strut to be slowly replaced by host tissue, and the homovital transplant—skin, kidneys, endocrines—which survive as functioning tissues. It is the latter which offers the greatest experimental challenge.

The observation reported by Medawar that a second graft from the same donor rabbit to the same recipient rabbit was rejected more rapidly than the first has sparked a great surge of interest in homotransplantation. The rejection phenomenon requires contact of host leucocytes with the homotransplanted tissues. This can be prevented by enclosing the tissue in the cell-impenetrable millipore chamber devised by Algire, whose name this now bears.

Hill, Border, Sicular, Brooks, and Moore were puzzled by the failure of permanent survival of endocrine tissues in the chamber. Their studies on the diffusion characteristics of various millipore filters have shown that the permeability coefficient of oxygen across the membrane is influenced by the thickness, since the pores cannot be enlarged without allowing leucocytes to pass. A thinner millipore filter is now available which allows greater diffusion. A corollary of this study was an evaluation of the oxygen needs of different tissues which bear directly on its transplantability in the chamber—liver and adrenal are least successful and have the highest oxygen need; thyroid and parathyroid are the most successful and have the least oxygen need. The suggestion has been made by Edgerton that in the absence of leucocytes the plumbing system within the chamber was inadequate and that as the weeks passed, cell debris accumulated which could not be disposed of.

Although the Algire chamber is a valuable experimental tool, there are shortcomings in its clinical usefulness. Further evidence of this fact has been reported by Swan, Hallin, Callaghan, Welch, and Friedman and Wilson, Zollinger, Mahan, and Brooks regarding the adaptability of dogs to the aparathyroid state. After removal of the chamber from these dogs after a period of 3 months or more there was no change in the animals' dependence or independence upon vitamin D, no change in general condition or calcium level, and no positive evidence of cell survival within the chamber. The hoped-for permanent function of endocrine tissue in these chambers, in the present state of knowledge, seems unlikely. Wilson cited 21 patients in whom endocrine tissues were transplanted, including thyroid, parathyroid, and ovarian tissues, with evidence, in a few, of temporary function only.

One of the unsolved mysteries of the homograft problem is whether there is an antibody response and whether the antibody can be identified. Terasaki, Cannon, and Longmire reported the following study. Serum from homografted chicks, injected with pooled spleen cells in one group and skin homografted in the other, showed a high incidence of strong agglutinating action on lymphocytes of normal chicks, whereas serum from normal chicks showed none. The process of clumping has been demonstrated by a time-lapse cinematography. More and more lymphocytes became firmly united despite vigorous cellular movement, a phenomenon quite different from the passive agglutinization of red cells. As the clumps enlarged, the cells in the center died and began to disintegrate.

One of the methods used to reduce the host-immune reaction was irradiation of the recipient. Brooke, Govaerts, and Murray studied the immunologic response to several antigens given intravenously and intradermally after sublethal doses of irradiation in the rabbit. The host response to any one antigen could not be correlated to the reaction to any of the others. However, the optimal time for antigen administration after radiation proved to be 24 hours. Skin grafts survived an average of 30 days, and the hemolysins from a prepared sheep antigen were decreased. Although the tuberculin reaction is considered analogous to the second set reaction observed in skin, no correlation was found in this study.

These are but a few of the recent reports of experimental and clinical progress which the plastic surgeon has found stimulating. Having advanced the extirpative era of surgery essentially to its limit, we are now in the midst of the reparative era. Advances, such as those described herein, may carry us over the threshold to the eagerly awaited replacement era.

GASTROINTESTINAL BILIARY CONDITIONS

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WITH FULL exploitation of the novelty of open heart and other cardiac surgery, interest has returned in healthful strength to other areas, and the field of gastrointestinal surgery is one of these. The wealth of material which should be included is overwhelming, and careful selection has necessarily been made.

Extension of studies on the transplantation of organs within the abdomen has raised some perplexing problems. Moore, Smith, Gruber, Demissianos, Burnap, and Dammin reported a series of liver replacements from donor dogs, aided in the procedure both by cooling and by shunts. Thereafter, liver function appeared to return, with production of bile and plasma albumin, and normal activity as to fibrinogen, urea, and carbohydrate metabolism. Lillehei, Goott, and Miller transplanted virtually all the small intestine from dog to dog, with good healing of anastomoses and return of function. In both sets of experiments, death followed rapid deterioration from apparent normalcy at a maximum of 6 to 8 days. The cellular structure of the liver and of the gut was essentially normal, without the vascular thrombosis of rejection of smaller tissue transplants. In both studies, the mechanism of death is still a mystery and challenge for further study.

Since the report of Brodie in 1903 of biochemical studies on perfused, excised rat livers, little had been attempted until the report of Otto, Pender, Cleary, Sensenig, and Welch which appeared last year, in which a dog was used for perfusion studies with the hope that an extracorporeal liver might be used for support in hepatic failure. At the 1958 Clinical Congress, Martinis, Goldsworthy, Jones, Nyhus, DeVito, Volwiler, and Harkins reported perfusions on the calf liver, and this year Demissianos, Sicular, Balankura, Kinney, and Moore and Kestens, Gerald, and McDermott, each in scholastic isolation long unaware of the activities of the other, performed more sophisticated perfusions of excised dog livers. All agree that oxygen use is less than normal, that bile is secreted, that bromsulphalein is cleared, and that other functions as well continue for hours.

That our knowledge of hepatic function can be expanded by such techniques is testified by Sokal. He found that isolated rat livers, perfused unfortunately without the precaution of asepsis, appear to maintain a normal blood sugar level in the absence of participation of neural or endocrine factors.

Laboratory studies of hepatic function require a method to determine hepatic blood flow which can be used repeatedly during a given experiment and which is independent of changes in hepatic cellular or reticuloendothelial function. Ballinger and Bartone reported a method in which all returning systemic blood is shunted around the inferior vena cava, which is ligated

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at a level just above the renals, permitting a sampling of mixed hepatic venous blood by a catheter passed into the inferior vena cava from above. Dye dilution curves permitted them to establish flow rates in a range of 50 to 60 milliliters per kilogram per minute, with a rather abrupt drop if the arterial mean blood pressure is reduced below 80 millimeters of mercury.

Several years ago Madden, Lore, Gerold, and Ravid called attention to the decreased hepatic venous cross section area of the liver in advanced cirrhosis. At the 1959 Clinical Congress, Carter, Barron, and Welch reported quantitation of the changes in the vascular compartments in cirrhosis by means of injection-digestion studies. Weights of injection media in relation to weights of whole livers showed a 50 per cent reduction in hepatic vein volume, a 14 per cent reduction in portal volume, and a slight increase in hepatic artery volume. It was suggested that this is an understandable aftermath of the inflammatory process of cirrhosis, the unsupported hepatic vein radicles, with low pressure, being most easily compressed by the advancing fibrosis of liver cell destruction, while the portal vein radicles normally have a higher pressure and are also supported and protected by the stroma of the portal triad. The thesis that the portal hypertension and ascites of cirrhosis are due to this reduction in the hepatic venous outflow tract was supported.

Disappointed with the ineffectiveness of glutamate and of arginine in ammonia intoxication, Orloff and Peskin reported animal studies on the administration of formaldehyde, which was found to combine even in blood with ammonia to form nontoxic methenamine. The slow intravenous infusion of formaldehyde proved more effective than arginine or glutamate in reducing the ammoniemia of Eck fistula dogs after ammonium citrate gavage. Further studies will precede clinical use.

McDermott presented an ammonia tolerance test for determination of adequacy of liver function and existence of shunts to the systemic circulation. It proved useful when hepatic compensation remained, but in severe liver damage failed to settle the existence of shunts. It would appear that this failure might result from such extrahepatic clearance as reported earlier by Bessman and Bradley and by Lawrence, Schwartz, Roberts, and Randall.

The mechanism of portal venous pressure reduction by pituitrin has perplexed many. Eiseman, Silen, and Tyler have done much to clarify the situation by end-to-side portacaval shunts in dogs, followed by measurement of changes in pressure and oxygen content of the portal system with pituitrin injection. The drop in pressure and the drop in oxygen content suggest that the effect of pituitrin is at least in part due to closure of submucosal gastroenteric arteriovenous shunts.

Although Kling and Allen reported the development of markedly dilated portal-systemic venous channels after gradual occlusion of the hepatic veins of the dog, it remained for Timaya and Thal to produce truly massive esophageal varices. This was accomplished by a two stage combination of splenic arteriovenous fistula and ligation of splenic venous return to the portal system. An interesting outgrowth of this study is the suggestion that arteriovenous shunting in the liver or portal system may be a factor in development of the clinical disease.

Several investigations concerning the pancreas were presented. From a physiologic point of view, Dumont and Mulholland demonstrated the addition of amylase, desoxyribonuclease, and lipase to the thoracic duct lymph in greater quantity than demonstrable in the plasma, after stimulation with secretin. This was especially true in the presence of pancreatic duct obstruction. They postulate utilization of this pathway in alteration of fat before entry into the blood stream.

From a pathogenic point of view, Hermann and Davis presented evidence of the production of the various types of pancreatitis seen clinically by the institution of partial obstruction of the canine pancreatic duct, an approach which has heretofore been unsuccessful.

Several approaches to the diagnosis of pancreatitis were also presented. These vary from excellent arteriographic studies by Frazer, Anlyan, and Baylin, which appeared to suffer by need of orientation by preliminary arteriogram in the dog, through evaluation of the Watson feces Ehrlich test by Rath, in which cancerous biliary obstruction was observed to become essentially complete within 10 days of onset of jaundice, to the use of antibody and enzyme blood tests.

Thal, Egner, and Murray have discovered specific pancreatic antibodies in experimental and clinical pancreatitis. Such antibodies also are found after injection of pancreatic tissue in

Freund's adjuvant into dogs and rabbits. All of 4 clinical patients suffering from proved pancreatitis showed such antibodies, but only 1 demonstrated true pancreatic autoantibodies. The implications of this finding are tremendous in the understanding of this disease. In the meantime, the precipitin test for pancreatic antibodies appears likely to become a useful diagnostic test for pancreatic disease.

Assay of serum enzymes has been helpful in the diagnosis of pancreatic disease, but the vagaries of serum amylase and trypsin determinations, in particular, are often clinically disconcerting. Pineda, Goldbarg, and Rutenburg undertook to evaluate the utilization of determination of beta-glucuronidase and of leucine aminopeptidase (LAP) in this connection in anicteric patients. Acute pancreatitis was associated with high levels of both enzymes, as was acute hepatitis. Cancer of the pancreas was associated in 94 per cent of cases with high LAP. These tests appear to be more reliable than bromsulphalein retention in liver disease and to offer some real help in the diagnosis of cancer of the body or tail of the pancreas.

Therapeutically, a possible avenue is suggested by the report of Bauer, Elliott, and Stewart that restitution of pancreatic function in the dog can be achieved after full-length opening of the gland into the duct, whether in the absence of prior disease or after induction of ductal obstruction. Some of many details in the technique are closure of the capsule only, over a slender tube placed in the duct, without effort to close gland substance or duct wall. The fate of obstructed ductal branches not laid open in this procedure is not yet clear.

Three papers of interest concerning the extrahepatic biliary tract were presented. Following the report of Imamoglu, Perry, Root, Crisp, Jenson, and Wangensteen in 1958 that gallstones can be made to develop in experimental animals by progressive obstruction of the cystic and terminal common bile ducts, a second method for the consistent production of bilirubin and cholesterol concretions was described by Imamoglu, S. L. Wangensteen, Root, Salmon, and Griffen. They have observed the development of such concretions in all female and most male rabbits treated daily with progesterone and diethylstilbestrol over a period of 40 weeks. On the thesis that stasis is a factor, they studied women by cholangiography late in pregnancy and early in the postpartum period and found filling and emptying to be greatly delayed as compared with a series of nulliparous women. It is suggested that the known frequency of gallstones in relation to pregnancy is secondary to this stasis.

Thomas and Linker reported work which promises to help the surgeon to recognize common bile duct stones. I^{131} rose bengal dye, upon intravenous injection, is excreted rapidly by the liver, is not absorbed from the gut, and is adsorbed upon common duct stones, especially pigment stones, in many times the concentration found in bile. With suitable probes now available to the surgeon in his common duct exploration, it appears likely that this technique will be of early practical help.

Madden and McCann reconfirmed their former report of uniformly successful end-to-end anastomoses of the common bile duct in a series of 8 patients, with follow-up periods of 6 months to 8 years (average 3½ years). The technique is supported by experiments in dogs and consists in meticulous fine silk suture without placement of catheters, T tubes, or splints, but with soft rubber drains to the area to remove minimal expected biliary leakage. Others have failed with techniques thought to be identical to this, and it is hoped that further study will uncover the fine points of difference which led to the success of Madden and McCann.

A series of excellent studies on gastric secretion were of interest. Redo, Barnes, and Ortiz reported the findings of a dialyzable component of gastric juice which is inhibitory to peptic digestion of the esophagus. One suspects this may be the same substance which Smith, DuVal, Joel, and Wolf described previously. They were able to prepare a solution which, on repeated parenteral injection into dogs, produced achlorhydria of long duration, coupled later with atrophic gastritis.

In 1956, Margolus and Harrison suggested that a hormone inhibitory to gastric acid secretion is released upon bathing one of a pair of isolated antral pouches with 0.1 normal hydrochloric acid. These experiments were repeated and presented by Shapira, Morgenstern, and State, but they found identical results on sham tests without acid bathing. Johnson, Cobo, Oberhelman, and Dragstedt also presented evidence casting doubt on the existence of an inhibitory hormone.

Nagano, Johnson, Cobo, Oberhelman, and Dragstedt confirmed the earlier finding by Sircus that distention of the duodenum produces a hormonal effect on gastric secretion similar to that of gastrin from the antrum. They found this effect to be modified by acid, phenergan, and secretin in a fashion similar to the antral effect.

Much interest is attached to the role of the pancreas in the control of gastric secretion. Work by Goelzer on the effect of pancreatectomy and by Greenlee, Nelson, and Dragstedt on total external pancreatic fistula suggests that exclusion of pancreatic secretions from the duodenum, with or without the removal of the pancreas, results in a several-fold increase in gastric secretory output.

Hinshaw, Branson, and Stafford postulated the high frequency of duodenal ulceration following gastroduodenostomy as due to failure of bathing of the duodenal mucosa by the alkaline secretions of the liver and pancreas, and they gathered evidence from canine experiments suggesting the wisdom of gastric anastomosis close to the ampulla of Vater.

Griffen, Salmon, Paterson, Costañeda, and Fattah set up experiments to show the importance of motion of gastric juice as a low pressure jet through the pylorus in producing ulceration. In control experiments in which identical gastric juices were gently irrigated through the duodenum, strikingly less ulceration occurred than in those in which it was introduced as an intermittent jet at a pressure of 30 centimeters of water. It is suggested that this may be a factor in the development of some clinical peptic ulcers.

Those in search of clarification of the many factors relating to the problem of postoperative peptic ulceration in the light of antral function were interested in the scientific exhibit of Chapman, Nyhus, and Harkins. After a careful review of all available data, they concluded that, if the antrum is to remain after an ulcer operation, it must be vagally denervated, it must remain in the acid stream, and antral stasis must be prevented.

That preservation of the pyloric sphincter may help to lessen the severity of dumping after Billroth I gastrectomies was suggested by the work of Flynn and Longmire and Rieger and Friesen. The former removed the mucosa from the pylorus and distal antrum and anastomosed in such fashion as to cover the raw area with mucosa from the upper gastric pouch. Rieger and Friesen performed sleeve resections. Both groups found long-term survivors to show fewer objective signs of dumping after glucose feedings than control dogs in which pyloric function had been abolished.

Lawrence and Mathews restudied the water shifts in the dumping syndrome, tagging separately red cells and albumin. Their data indicate a shift of water from red cells as well as from the plasma, and furthermore they indicate that the water shifts are not large enough to explain the cardiovascular sequelae of the dumping syndrome. These conclusions are in striking agreement with Morris, Greenfield, Jordan, Peddie, Gordon, and DeBakey who found a rise instead of the anticipated fall in renal blood flow during dumping, a change which is not explicable upon the basis of decreased circulating blood volume.

It is possible that a part of the explanation of these findings may be found in the work of O'Hara, Fox, and Cole. They found serotonin in the gut and blood stream after irrigation of the upper small intestine with hypotonic, isotonic, and particularly hypertonic sugar solutions. Five-hydroxyindoleacetic acid was found in the urine of some volunteers who had had sugar solutions placed in the jejunum by tube. Discussion revealed that DeBakey and his colleagues had sought this substance in the urine of patients with dumping syndrome and had failed to find it. It appears that some such mechanism must be at work. This field is open for further investigation.

A convincing study on the use of serum lactic acid dehydrogenase in the diagnosis of necrosis of gut was presented by Braun, Harris, and Sherman. Rothenberg, Chassin, Sher, and Lear established that in dogs a combination of antibiotics and resection of the underlying intestinal leak makes possible reasonably safe primary anastomosis in the face of peritonitis. Cohn and Beauclair convincingly showed that kanamycin is the safest of the broad spectrum antibiotics to use therapeutically in the abdomen.

Many other excellent reports of investigations on a variety of subjects were presented. One of these was provocative as a strikingly new avenue of approach. Stafford, Schnaufer, and Cone constructed true, or circular, closed intestinal loops in dogs, using the lower one-half of the small intestine and the upper one-half of the colon, anastomosing the ends together, and by a

second anastomosis restoring continuity to the rest of the gut. Without antibiotics these dogs died in a few days, but with 1 gram of neomycin in the loop some have lived as long as 5 months. They do not become icteric, bile at least in some does not accumulate in the loop, and there is no abnormal appearance of bilirubin waste products in the excreta. Bile pigment is, therefore, apparently disposed of by some still unknown mechanism. The preparation offers an exciting opportunity to resolve many problems in pigment metabolism.

TUMORS

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BEFORE ONE of the sessions on tumors at the 1958 Clinical Congress, Sir Stanford Cade predicted that research in cancer would be increasingly directed toward "the soil instead of the seed." He suggested that areas of fruitful investigation would deal with the host, that is, the environment in which the cancer is born and grows.

At least 6 of the 24 papers presented at the 1959 sessions on tumor dealt directly with alterations of the host in order to influence experimental tumor growth. One such experiment by Fisher and Fisher of Pittsburgh studied the effect of nutritional factors upon the growth of artificially induced hepatic metastases. Using the Walker 256 carcinosarcoma tumor injected into the portal vein of rats, they studied the incidence of artificial metastases in groups of animals on diets with varying amounts of protein. All diets were isocaloric. On a nonprotein diet there were 18 per cent metastases, on an 18 per cent protein diet, 35 per cent metastases, and on a 30 per cent protein diet, 60 per cent metastases. While these results are of themselves most interesting, they also point up a very important factor to all interested in tumor research in animals, namely, that it is of crucial importance that the diet of experimental animals be scrupulously controlled. It is not enough to know that the control and experimental groups are maintaining the same weight. One must know that the food consumption is identical and of the same composition.

Griffith has altered the host by cold stress and hypothermia. He found that both in rats subjected to severe cold in the conscious state and in animals subjected to hypothermia tumor takes were much higher in the stressed animals. Tumor take was 96 per cent and 92 per cent in the experimental groups as compared to 72 per cent and 58 per cent, respectively, in the control groups. It would seem possible that these results may have been due to alterations in adrenal functions. The experiment repeated in adrenalectomized animals would be interesting.

The immunologic response of the host to trauma has been the subject of an increasing number of studies. It would appear that immunology offers one of the best hopes for the control of cancer.

Schrek, Jackson, Henegar, and Preston, using Bagg's rat tumor reported that they found no adverse effect on host resistance to be produced by nitrogen mustard and that furthermore nitrogen mustard in combination with Bagg's tumor seemed to provide a more potent antigen than tumor alone. Preston, Jackson, and Henegar, using the same Bagg's tumor, found evidence to indicate that living lymphocytes and living testicle cells, prepared from tumor-immune animals, are cytotoxic to the Bagg's tumor.

One of the most exciting reports presented at the Forum sessions on tumor was that of Grace, DiPaolo, Mirand, and Haas. They have produced tumors in animals in which the spontaneous incidence of cancer is essentially nil by injecting them with the sterile cell-free filtrate of human tumors freshly removed at operation or autopsy. The filtrate was injected into newborn mice and hamsters. It is essential that newborn animals be used because it is most important that the injections be made before the ability of the animal to respond immunologically has developed. Only .1 milliliter of the sterile cell-free filtrate was injected into mice and .2 milliliter

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into hamsters. The animals have been observed from 3½ months to 9 months after injection. Tumors, frequently at multiple sites, have developed in many of the mice after the injection of filtrates from many types of human tumors. To date no tumors have developed in hamsters. The induced tumors do not resemble, either grossly or microscopically, the human tumor from which the filtrates were made. The filtrate from patients with acute leukemia most often produced tumors in animals but many varieties of human tumors induced animal tumors. The most commonly induced tumor was adenocarcinoma of the breast. Control animals inoculated with filtrates of normal organs from patients without cancer have not produced tumors after 9 months of observation. An interesting phenomenon was noted in 1 female animal in which a tumor developed during pregnancy. It regressed after parturition only to reappear at a subsequent pregnancy.

Grace reported that his group recently succeeded in producing tumors in mice with cell-free filtrates of normal organs from mice with breast tumors induced by cell-free filtrates of human tumors. Grace concluded "that subcellular particles from a variety of human neoplasms can induce tumors in young Swiss ICR mice." These findings confirm and extend the work of Gross, Stewart, Kaplan, and Schwartz.

Gross and Kaplan have produced lymphomatous tumors in mice by x-radiation. Sterile cell-free filtrates of these tumors, when injected into newborn mice of the same strain, induce tumors. These experiments demonstrate that from tumors induced by a physical agent a substance may be obtained which will induce tumors in other animals of the same species. They suggest the relationship between physical carcinogenic agents and a "virus."

Graham and Graham have recently reported on the use of a vaccine made from the patient's own tumor. They have utilized the principle of an adjuvant to potentiate the antigenicity of the tumor vaccine. Freund's adjuvant was used. They reported having used this autovaccine on 114 patients. Most of the patients had either cervical or ovarian carcinoma. The Grahams make no extravagant claims for the vaccine. However, a small number of patients, 14 per cent, are apparently free of disease. Furthermore, it appeared to them that the vaccine might have potentiated the effect of radiotherapy given after the vaccine. While no one could regard these results as startling, they further support the immunologic aspects of cancer and should be continued.

Hoye and Smith have succeeded in setting up an experimental system to study alterations in transplantable tumors produced by small amounts of x-radiation. Using a variety of mouse tumors, they demonstrated that amounts of x-radiation insufficient to kill the primary tumor did alter the tumor so that the number of metastases which the tumor produced when transplanted intravenously into fresh mice was markedly reduced. The method may prove to be a very useful tool for further study.

While these reports are examples of the current attack on the frontiers of the cancer problem, many others were presented which dealt with finding techniques and better methods of treating cancer with our present therapeutic mechanisms.

Krementz and his group expanded studies previously reported by others on the effectiveness of various agents in cleansing open wounds of cancer cells. T.S.P.A. was used in this instance with some effect but was not entirely satisfactory. However, their data again demonstrated that irrigation of a wound with ordinary physiologic saline is completely ineffective in destroying or removing cancer cells. Others have shown that irrigation with saline of a wound contaminated with cancer cells may actually increase the likelihood of the implantation and growth of the cells.

In recent years much attention has been paid to the isolation of cancer cells in the circulating blood. Watne has extended the technique and has collected lymph from the thoracic duct in patients with cancer. He has been able to isolate cancer cells from the thoracic duct lymph in 22 per cent of the patients studied. These included cancer of the stomach, lung, pancreas, gallbladder, and breast. It is curious that in 8 patients with cancer of the colon or rectum he was unable to find cancer cells in the thoracic duct lymph. He has studied the fate of the cells in the lymph during the course of surgery and chemotherapy.

Advancing techniques in other areas of surgery have provided the surgeon interested in the treatment of cancer with another tool, namely, isolated perfusion techniques for the administration of chemotherapeutic agents.

The technique has been reported at this meeting as having been applied to almost every area of the body. Ausman and Aust described a technique for isolated perfusion of the liver. They had successfully used the technique on 3 patients.

In an exhibit, Creech, Krementz, and Reemtsma presented their techniques, dosages, and results. They have perfused 169 patients 189 times. About 50 per cent of the patients with melanoma who have been perfused remained quiescent, while in only 20 per cent of patients with carcinoma has the disease remained quiescent. The technique of local perfusion has promise but must await the discovery of the ideal anticancer agent.

Curreri in an exhibit has reported the results of the use of fluoropyrimidines on 185 patients. He estimated that 48 or 25.9 per cent of these patients were improved. The white blood count fell to below 5,000 in all but 27 of the patients. The drug seemed to be most effective against cancer of the breast.

A panel discussion on cancer of the head and neck led by Klopp used brief case histories and short movie strips to illustrate common types of head and neck cancer. The panel was unable to agree completely about the timing of radical neck dissection in papillary carcinoma of the thyroid.

The role of extended excisional surgery in early and late cancer was the subject of a panel led by Slaughter. In general, the panel agreed that there is often undue pessimism on the part of surgeons particularly with respect to head and neck cancer. The view was expressed that extensive surgery was indicated in many of the massive lesions in this area.

Bricker reported a 50 per cent 5 year survival rate for carcinoma of the rectum, which had invaded the genitourinary tract, treated by total pelvic evisceration. He recommended an "all or none" policy with regard to pelvic evisceration. If such surgery is at all indicated, a total pelvic evisceration should be done.

Some workers have expressed the opinion that the time of treatment in carcinoma is unimportant. Apparently statistics can be mustered to support such a view. However, until more of the biologic activity of the tumor and the protective mechanisms of the host are known, and until it can be predicted in which particular patient a delay in therapy is harmless, most surgeons would agree that all cancer should be treated with a sense of urgency. Even though some argued at the Clinical Congress that early detection of cancer does not appreciably alter survival rates, early detection and prompt therapy remain our best weapons against cancer.

UROLOGY

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LABORATORY and clinical investigations in urology have resulted in new and important developments during the past year.

In some patients, after operation, respiratory acidosis occurs together with a decrease in renal function. To see whether a possible relationship exists between these two conditions, W. J. Brooker, J. S. Ansell, and E. B. Brown have studied the effect of respiratory acidosis, induced in dogs by inhalation of carbon dioxide, upon urinary output and renal blood flow, which they measured by means of an electromagnetic flow meter applied to the renal artery and vein. In all of the animals there resulted oliguria, cyanosis, and a marked decrease in renal blood flow. This decrease in renal blood flow seemed to be unrelated to a concomitant fall in systemic blood pressure and was found to be the result of an increase in renal resistance to blood flow during hypercapnia. This study showed that renal blood flow could be measured directly by this method, and that a relationship does exist between high blood carbon dioxide concentration on the one hand and renal blood flow and oliguria on the other.

The basic cause of lower nephron nephrosis, or acute tubular necrosis, following trauma, has been attributed by some investigators to poison-

ing by tissue toxins and hemoglobin pigments. William Hostnik, Samuel R. Powers, Jr., Antonio Boba, and Arthur Stein in a controlled study measured the renal blood flow in dogs by means of a double lumen catheter in the vena cava below the renal veins, after occluding the cava above. After producing mallet trauma to the thigh they observed pronounced and sustained renal vasoconstriction. This vasoconstriction was prevented in one group of traumatized dogs by first giving intravenous mannitol, an osmotic diuretic, which increased the renal blood flow and maintained the urinary output.

In a second group of traumatized dogs the oxygen tension in the renal vein remained constant whereas the oxygen tension in the urine fell markedly, and the renal vascular resistance rose. These observations showed that the distal tubules had been deprived of oxygen but the authors were unable to identify an actual shunting mechanism in the renal vascular bed.

Histologic studies of the anoxic kidneys were not reported, but it would seem that this work has confirmed the previous report of Powers, Boba, and Stein on the presence of renal vasoconstriction following crush injury, and its effect on the tubules.

Edward J. Fedor, Sil H. Lee, and Bernard Fisher have used renograms in dogs after the intravenous injection of radioactive diodrast to determine the exact time of rejection of a renal homotransplant and to distinguish between technical failure and rejection as such. It seemed obvious that a surgical technique that failed with an autotransplant could not be expected to succeed with a homotransplant, regardless of immunologic factors.

Renograms in 19 autotransplants and in 15 homotransplants were made at comparable intervals after the recipient's normal kidneys were removed. Blood urea nitrogen and creatinine levels were also determined, urine collections made, and specific gravities recorded.

The renograms showed the three characteristic segments: the vascular, representing the appearance of the radioactive compound in the blood vessels of the kidney; the secretory, reflecting tubular cell secretory function; and the excretory, reflecting the excretory phase of renal function.

For approximately 7 days both groups showed similar tracings; vascular and secretory phases remained adequate, but there was a deterioration in the excretory phase. Between 7 and 12 days after operation the autograft tracings became normal, but in the homotransplants the rejection phenomenon then became evident, with continued deterioration in the excretory phase, and with beginning alterations in the other two phases. However, the hazards to the dog of daily anesthesia and narcotization convinced the authors that the evaluation of these renograms had little to offer over the standard tests of renal function in following a homotransplant.

The role of the lymphatics in experimental pyelonephritis has been studied by J. J. Murphy, Harry W. Schoenberg, William H. Rattner, and Ralph H. Scott. After unilateral ligation of the hilar lymphatics in 5 rabbits and 5 dogs, they injected coliform bacilli intravenously. Acute pyelonephritis appeared in the treated kidney in 3 of the rabbits and in 2 of the dogs, but the untreated kidney remained uninfected. These results suggested that the lymphatic obstruction had rendered the kidney more susceptible to circulating organisms.

In another group of dogs they injected one renal artery with virulent staphylococci and produced pyelonephritis. They then injected a dye into the pelvis, first of the infected kidney and then of the normal kidney under pressure. The dye appeared in the cisternal lymph from only 1 of the 8 infected kidneys, whereas it appeared promptly from the pelves of all the normal control kidneys. This observation indicated an intrarenal lymphatic obstruction produced by the staphylococcal infection, which left the kidney more susceptible to circulating bacilli.

These authors also studied the pathway of ascending renal infection in 15 dogs. They injected into the bladder a suspension of carbon particles and maintained a high intravesical pressure for several hours. Carbon particles then were found in the periureteral lymphatics at varying distances above the bladder, and even in the peritubular spaces and hilar nodes. Reflux through the lumen of the ureter did not occur. They conclude that bladder neck obstruction may result in the "pumping" of particulate matter from the bladder to the kidney through the periureteral lymphatics, and that the catheter, which recently has been so maligned, is not the usual cause of pyelonephritis in man.

The entrance of bacteria into the general circulation from the genitourinary tract is said to be

the cause of bacteremic shock in 50 to 75 per cent of such cases, and prior operative or diagnostic instrumentation is the usual cause of the bacteremia. Mortality in bacteremic shock is reported to vary from 25 to 75 per cent, with an average of about 65 per cent, despite vigorous antibacterial therapy, possibly because the hypotension may escape notice for some hours and then may not respond to parenteral vasoconstrictor drugs.

Abraham T. Cockett and Willard E. Goodwin treated 11 patients in bacteremic shock by reducing the body temperature to from 93 to 97 degrees F. for 48 to 72 hours, in addition to giving kanamycin, 1 gram per 24 hours, together with corticosteroids, whole blood, oxygen, and vasopressors sufficient to maintain the systolic blood pressure at a level of 90 to 110 millimeters of mercury. Improvement was striking in 48 hours in 4, and complete recovery was achieved in 10 of the 11 patients.

Since it is frequently necessary to open a kidney for the extraction of a large stone, and this kidney may be solitary, surgeons want to know how long the renal vessels can be occluded before renal damage occurs.

Paul J. Stueber, Simon Koletsky, and Lester Persky studied the effects of intermittent clamping of the vascular pedicle of an intact solitary kidney in 3 groups of anesthetized dogs. Occlusions of 30 minutes each were alternated with 10 minutes of free flow. No permanent or significant renal changes occurred after the pedicle had been clamped for a total period of 90 minutes, but four 30 minute periods of intermittent clamping caused marked elevation of blood urea nitrogen, and distorted histologic appearance was present up to 2 months later. These results differ slightly from those of Scheibe and his associates who found that the renal pedicle in the dog could be occluded for 2 hours with expectation of recovery. The restoration of free flow, therefore, after each 30 minute period of occlusion does not seem to improve the viability of the dog's kidney.

Phillip P. Porch, Neil O. Chamberlain, and William H. Edwards have approached the problem differently. After contralateral nephrectomy they occluded the renal vein in dogs for periods varying from 30 minutes to 3 hours. Histologic changes were reversible if the vein was occluded for less than 90 minutes. Similarly, simple arterial occlusion up to 2 hours resulted in no permanent damage in most cases. When contralateral nephrectomy was postponed for 3 weeks to allow the affected kidney to recover, arterial occlusion for 3 hours was fairly well tolerated. This conclusion confirms that of others, namely, that a given amount of damage is produced in a shorter time by venous occlusion than by arterial occlusion.

The occurrence of urinary incontinence in many women, and in some men after operation or trauma, has led Jack Lapides, Edward R. Ajemian, Bruce H. Stewart, and John R. Lichtwardt to study bladder pressures and urinary sphincter resistances in a variety of situations. These investigators believe that their studies show that the sphincter is a tube composed of smooth muscle and elastic tissue and comprises the proximal 3 centimeters of the urethra in both sexes. Under resting conditions urinary control is maintained by the tonicity of the wall of the tube, but on exertion this tubular resistance is increased by the contraction of the pelvic and perineal striated muscles which compress the tube and also elongate it. They conclude that the primary defect in most cases of female stress incontinence is a shortening of the urethra which is more pronounced when the patient stands, and they have been able to provide a functioning sphincter by constructing a tube from the bladder wall. General conclusions that might be drawn from these studies are: that adequate lengthening of the urethra by surgical suspension should cure most cases of simple stress incontinence in the female; that surgical removal of bladder neck obstruction in women should not be permitted to result in a urethra shorter than 3 centimeters; and that relief of prostatic obstruction in males should not cause damage to the apical prostatic urethra and membranous urethra.

Another type of urinary incontinence exists with exstrophy of the bladder, a deformity very difficult to correct. Most urologists have recommended cystectomy in these cases combined with some form of urinary diversion, but interest continues in the development of a satisfactory method of plastic repair. John K. Lattimer, Archie Dean, Jr., and Louis J. Dougherty have repaired the defect in more than 20 young children 6 months old or older, but report postoperative reflux of urine into one or both ureters in all cases, as well as some degree of urinary incontinence, varying from slight stress in 2 cases to considerable leakage in others. These investigators believe that their procedure gives these children at least a

partial respite from most of their difficulties and does not preclude subsequent urinary diversion if urinary control is not eventually acquired. They do not advise an attempt to obtain complete urinary control at the initial operation because the resulting increase in intravesical pressure might cause progressive urinary reflux. Bilateral iliac osteotomy was sometimes used to facilitate the soft tissue approximation and was carried out when possible about 7 days before the plastic repair, and before the child was 2 years old.

In an attempt to obviate urinary reflux, ascending infection, and reabsorption of urinary constituents, M. Bogash, F. P. Kohler, R. H. Scott, and J. J. Murphy, have investigated the feasibility of using a plastic bladder as a substitute for the urinary bladder of dogs. They have found that a specially constructed valve, when attached to the lower end of the ureter and implanted into the normal bladder, provides good ureteral drainage and prevents infection and reflux. However, when the ureters of dogs were implanted into the plastic bladders by means of these valves, hydronephrosis and renal failure uniformly developed. The reason for the failure of the valves when used with the plastic bladder is not apparent at the moment and is undergoing further study. Another problem that will require attention is the development of a warning device which will indicate a full prosthesis and the need to empty it.

At present, there is widespread interest in the development of various types of bladder substitutes, made from segments of bowel, that may function satisfactorily after total cystectomy for carcinoma.

Failures as well as successes have followed the construction of urinary pouches from portions of both large and small intestine, and Sidney R. Weinberg, Benjamin Peng, and Arthur Ullman set out to answer by experimental study the following questions: (1) Which method of implanting the ureter into the pouch is the most satisfactory? (2) Does the fluid capacity of a doubled loop of bowel exceed that of a single loop? (3) Does an isolated segment of sigmoid make a better bladder substitution than does a segment of ileum?

They found: (1) the most satisfactory method of implanting the ureter consisted of laying it in a submucosal trough and anastomosing its end to an opening made in the submucosa and mucosa of the bowel; (2) vesical capacity was not increased by use of a doubled loop of ileum, as compared with a single loop; and (3) a sigmoid segment was more satisfactory than an ileal segment as a substitute bladder, since the average reabsorption of electrolytes was less with the sigmoid bladder, and the postoperative urograms and survival rates were significantly better. Three patients have been given a sigmoid bladder, and one of these at the end of 1 year is alive and well.

A considerable amount of work, however, remains to be done before one would seem justified in recommending this as a routine procedure after a time-consuming complete cystectomy for carcinoma.

One of the commonest causes of failure with many operations for diversion of the urinary stream above the bladder has been the constant absorption of urinary products through the intestinal mucosa, which causes chemical imbalance. Gilbert, Pace, and Izant successfully transplanted autogenous bladder mucosal grafts to segments of bowel from which its mucosa had been stripped. The objective of that procedure was to provide a urinary receptacle that was a nonabsorptive pouch.

These workers now have sought to determine whether such intestinal segments, lined with vesical instead of bowel mucosa and sewed to the dome of the canine bladder, would absorb radioactive iodine, the absorption of which has been found to be representative of that of other ions. These prepared bladders absorbed no more radioactive iodine than did the bladders of normal dogs, in contradistinction to the very marked absorption found in dogs after ileocystoplasty with intact ileal mucosa. This study indicates that an intestinal segment when lined by bladder mucosa and employed as a urinary reservoir will absorb no more ions than will a normal bladder.

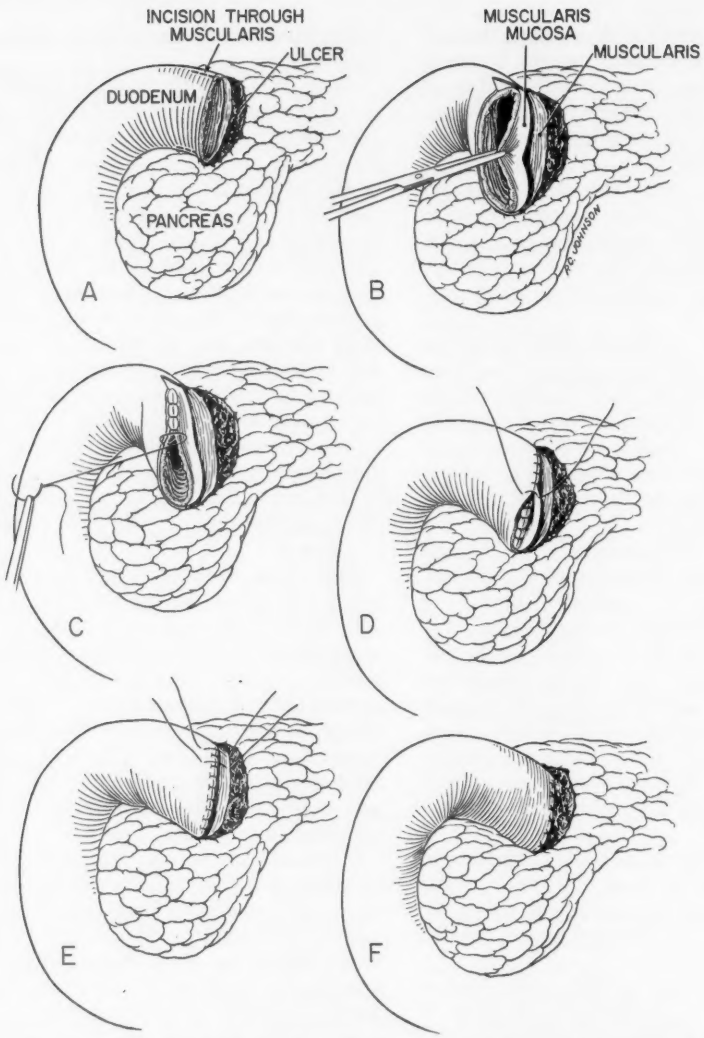

FIG. 1. A, The duodenum has been divided at the inferior margin of the ulcer and incisions made superiorly and inferiorly down to the muscularis mucosa. B, Development of the posterior plane between muscularis mucosa and muscular coat. C, Closure of the mucosa with a fine continuous absorbable suture. D, Approximation of the muscularis mucosa posteriorly to the anterior seromuscular coat using interrupted nonabsorbable sutures. E, Approximation of the anterior seromuscular coat to the posterior muscular layer fused to the pancreas with interrupted nonabsorbable sutures. F, Completed closure.

Intramural Dissection and Staggered Closure of the Duodenal Stump.—Louis R. Slattery.

THE SURGEON AT WORK

INTRAMURAL DISSECTION AND STAGGERED CLOSURE OF THE DUODENAL STUMP

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CLOSURE of the duodenal stump is still a difficult problem in subtotal gastrectomy performed for chronic duodenal ulcers which have penetrated through the duodenal wall into the head of the pancreas and the gastrohepatic ligament. Removal of the duodenum to the inferior margin of the ulcer is easily performed, the problem being to dissect an adequate cuff of duodenum distally for closure. It is during this step that injury may occur to the pancreas, accessory pancreatic duct, or common bile duct. These hazards have been avoided by suturing the anterior duodenal wall to the fibrosed lower margin of the ulcer bed. If a short fibrosed segment of duodenum has resulted from dissection and a poor inversion obtained, catheter duodenostomy has been practiced. Neither of these methods is as satisfactory as the method which involves a secure closure in layers.

The foreshortening of the duodenum caused by chronic penetrating ulcers is principally in the posterior half of the bowel circumference where the inflammatory process about the ulcer produces a fusion of the muscular coat to the pancreatic capsule. Release of the posterior half of the circumference through the plane between the muscularis mucosa and muscular coat leaves the muscular coat on the pancreas and permits dissection of adequate tissue for closure without endangering important structures. A staggered closure allows utilization of all layers without the difficulties and insecurity inherent in attempting to invert a rigid fibrosed posterior duodenal wall.

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Although this closure must have been done unwittingly or accidentally many times, review of the literature revealed no previous description. Laprell has called attention to the same pathologic findings, but the subserous dissection described and illustrated indicates detachment of the entire thickness of the bowel from the pancreas.

TECHNIQUE

After section of the duodenum at the inferior margin of the ulcer, incisions 1 centimeter in length are made superiorly and inferiorly through the muscular coat down to the muscularis mucosa. Blunt dissection with the point of a hemostat in the plane between muscularis and muscularis mucosa around the posterior half of the duodenum mobilizes a tough cuff of normal tissue and leaves the muscular coat on the pancreas. This release is almost avascular and necessitates division of only 2 or 3 tiny vessels running between the muscularis and muscularis mucosa which can be easily secured and ligated. After trimming away any traumatized tissue from the end of the duodenum incidental to the dissection, the mucosa is closed as a single layer with a continuous fine absorbable suture. This procedure provides hemostasis, eliminates the redundancy obscuring other layers, and furnishes a layer which can be much more easily inverted than one including a greater thickness of intestinal wall. The posterior muscularis mucosa is approximated to the anterior muscularis with a layer of interrupted nonabsorbable sutures to invert the mucosa. Closure is completed by approximation of the anterior seromuscular coat to

the posterior muscular coat in its fused position on the pancreas with a layer of interrupted nonabsorbable sutures. The final step is completed with ease, as the normal anterior wall of the duodenum can be readily brought over to the muscularis.

CONCLUSIONS

A method has been described for use in the difficult closure of the duodenal stump in layers. Intramural dissection of the posterior wall avoids injury to important structures. A staggered closure permits inversion of uninflamed tissues. Tension is avoided, and all layers of the tissue are utilized.

REFERENCE

1. Laprell, H. Der Duodenalverschluss beim penetrienden Ulcus duodeni unter Bildung eines Schleimhautmuskelzylinders. Chirurgia, 1955, 26: 404.

A METHOD FOR THE REMOVAL OF THE ADHERENT DISTAL THROMBUS

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IT HAS BEEN AMPLY DEMONSTRATED that successful embolectomy depends upon an open distal arterial tree, and therefore careful attention must be given to the removal of distal propagating clot, if present. Retrograde flushing from an arteriotomy beyond the thrombus has proved to be of great value in accomplishing this, and has significantly extended the applicability of embolectomy to late cases and to emboli lodging at the bifurcations of the brachial and popliteal artery. Between 1 and 2 days after its appearance, however, distal thrombus begins to become adherent to the wall of the vessel and it becomes increasingly difficult to remove the clot by flushing. In larger vessels, clot may readily be removed by the use of conventional thromboendarterectomy strippers, but complete removal of adherent thrombus from smaller arteries, particularly the tibial arteries, still presents a problem. A simple instrument, easily constructed in the home workshop, which has been used successfully in the removal of adherent thrombus below the popliteal artery bifurcation is described herein.

The instrument is shown in Figure 1. It consists of an 18 inch length of No. 22 surgical stainless steel wire with a 1 to 2 millimeter bead of silver solder fused to either end to avoid perforating the vessel wall. A helix of about three turns is constructed on one end of the wire by wrapping it about a 1/16 inch rod and removing the rod. The straight end of the instrument is inserted through the needle hole used for retrograde flushing in the distal artery, for example, the posterior tibial artery at the ankle, and is passed as a probe up the artery and out a proximal arteriotomy in the parent vessel. The helical portion of the instrument is then screwed into the lumen of the vessel through the needle hole by rotating the proximal end of the instrument, and it is then drawn up the artery and out the proximal arteriotomy. The outer diameter of the helix is slightly larger than the internal diameter of the vessel but the separation of the turns of the helix allows the vessel to conform to the shape of the helix and thus not be ruptured. The smooth wire of the helix in passage effectively separates the thrombus from the arterial wall in the same manner as does a thromboendarterectomy stripper (Fig. 2). Usually the entire clot will be withdrawn with the helix, but a second passage may be necessary to remove dislodged fragments. Clot can be extracted without a distal arterotomy, using the instrument like a corkscrew.

An instance of the instrument's use is presented in the following case.

CASE REPORT

A 60 year old man suffered an embolus to the bifurcation of the aorta 10 days after a posterior myocardial infarction. At operation, 6 hours after embolization the saddle embolus was removed with the restoration of good femoral pulses but persistence of severe ischemia of the feet. Femoral arteriograms revealed filling of both superficial femoral and popliteal arteries but, due to the timing of the injection, the distal vessels were not demonstrated. Both popliteal arteries were explored and pulses were palpable both in them and in the proximal tibial arteries that could be felt through the incisions. The persistent ischemia of the feet was thought to be due to arterial spasm, and this indeed was the case in the left leg which 3 days after opera-

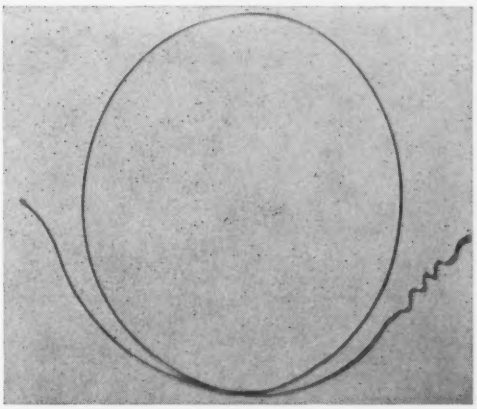

FIG. 1. Instrument for the removal of adherent distal thrombus.

Supported by U. S. Public Health Grant H-633(C8).

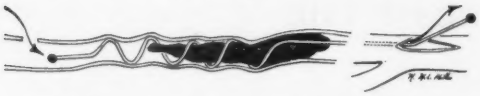

FIG. 2. Rounded coils of the wire helix bluntly separate thrombus from endothelium as the instrument is drawn through the vessel.

tion was of good color with a palpable posterior tibial pulse at the ankle. The right foot, however, failed to improve, and 5 days after operation showed deep cyanosis of the entire forefoot with beginning ischemic extravasation of blood in the dermis in this region. There was a temperature level at the malleoli and sensation in the toes was lacking. Review of the previous arteriogram showed thrombus within the right superficial femoral artery with blood flowing around it. The right popliteal artery was re-explored on the sixth postoperative day. An arteriotomy revealed no thrombosis within the popliteal artery itself. There was fairly forceful bleeding from the proximal end of the artery and slight bleeding from the distal end. The posterior tibial artery at the ankle was exposed and thrombosis was not present. Retrograde flushing and passage of a ureteral catheter and a knotted No. 0 chromic catgut tie up the posterior tibial artery failed to yield any thrombus. With the instrument described a 4 inch length of thrombus was extracted from the posterior tibial artery, and with a thromboendarterectomy stripper, a 4 inch mural thrombus was removed from the proximal femoral artery. Upon closure of all arteriotomies, there was an excellent posterior tibial pulse. Warmth and color returned to the forefoot within 24 hours.

An injury of the digits of the foot resembling frostbite resulted and there was good circulation at the base of the toes. The posterior tibial pulse disappeared 1 month after operation, at which time the patient was ambulatory, without change in the popliteal pulse or apparent change in the circulation of the foot. At the last follow-up visit 5 months after surgery, he had returned to work, and pain had disappeared but the foot was hyperesthetic.

THE SURGEON'S LIBRARY

Reviews of New Books

THE HIGHLY ILLUSTRATED volume *Quadri Arteriografici*[1] describes the characteristics of contrast medium visualization of the arterial system in a variety of pathologic processes. A brief history of the application of arteriography highlights the major steps in the present development of the method. The technique of the authors is presented in some detail, and the indications and contraindications of arteriography are briefly touched upon.

The normal anatomy of the arterial systems of the pelvis, upper extremity, and lower extremity are presented in the two-dimensional relationship which is seen in the usual one-plane roentgenogram.

The changes in the aortogram and arteriogram which are found in the presence of Buerger's disease, arteriosclerosis obliterans, congenital arteriovenous fistulas, and the syndrome of Malan are illustrated. In these sections, the reproductions of the numerous roentgenographic plates are excellent. The anatomic location of the various changes is thoroughly described to an extent which is, perhaps, not yet so completely developed by most roentgenologists. There are several interesting roentgenograms which illustrate cases of congenital arteriovenous fistulas.

In general, the illustrations in their clarity of reproduction and the analysis from the standpoint of anatomic completeness establishes a high standard of excellence. —*Ormand Julian.*

THE SECOND EDITION of *The Neurologic Examination,*[2] coming so soon after the first, testifies to the soundness of planning of the earlier volume and to the continued healthy growth of the field of neurology. This is a medical discipline which has expanded rapidly in the past 10 years after reaching an almost moribund state in the postwar period. The development of the science of communication and of new apparatus for research opened up broad fields of investigation regarding the nervous system with the result that a large new anatomy and physiology had grown up. This moved rapidly into the field of normal human behavior, as well as that of the abnormal, so that old textbooks had to be revised and more than that, the approach to the examination of the nervous system required considerable overhauling. Therefore, with respect for the past and with an eye for the future, DeJong prepared the first edition. As a teacher of neurology, as a research scientist, and as editor of one of the most active journals in the field, he was conversant with the advances and was in a position to screen out that which would be lasting and useful. These data have now been woven into this new volume.

As previously, the basic principle has been followed that the examination of the nervous system must perforce be based on appreciation of neuroanatomy and neurophysiology. New techniques of communicating with patients are depicted, whether it be difficulty of expressive communication, as in aphasia, or in receptive communication, as in one of the agnosias. Thus, the phenomena of human behavior has been tied up with the physiology of the nervous system. In addition, procedures have been described involving the use of the modern electronic machine which has been adapted for human engineering. Heretofore, these were exclusively limited to the research laboratory; now the author has helped to establish their place in the clinical examination. Thus, the electroencephalograph, the electromyograph, the special devices for measuring acoustic function, and others are all well described. The heretofore hard-to-understand systems, such as extrapyramidal, the reticular formation, are now a part of clinical neurophysiology.

The book is generously illustrated with new photographs, and every chapter is documented with a significant, up to date bibliography. Again, while respect is given to the past, the originator of a sign or of a technique, the interpretation is brought up for current evaluation. The names of old, as well as the new, contributors are faithfully listed in each reference section.

Out of all of this comes an important contribution to American medicine, a book, almost encyclopedic in scope, for use in the examination of that all important mechanism which gives the human being his exclusive quality, the nervous system. Despite the size of the tome and detailed contents, it reads easily and, therefore, can be used by all, whether it be the sophomore student in neurodiagnosis, the neurophysiologist who wishes a clinical frame of reference, the general practitioner who would like to understand why he does what in examining a patient, or the specialist in

[1] QUADRI ARTERIOGRAFICI. By Edmondo Malan. With the collaboration of G. Tattoni, C. Malchiodi, G. Bounous, and U. Ruberti. 124 pages, 81 illustrations. L. 5,000. Torino: Edizioni Minerva Medica, 1958.

[2] THE NEUROLOGIC EXAMINATION. Incorporating the Fundamentals of Neuroanatomy and Neurophysiology. By Russell N. DeJong, M.D. 2nd ed. 1,078 pages, 368 illustrations. $20.00. New York: Hoeber-Harper, Inc., 1958.

the diseases of the nervous system who would like an introduction into the profundities of this complex communicating mechanism. The second edition is a great step forward beyond the excellent, well accepted, first edition. —*Benjamin Boshes.*

THE PUBLICATION entitled *The Contributions of Dr. C. C. Guthrie to Vascular Surgery*[3] is a tribute to a contemporary surgeon who is Emeritus Professor of Physiology and Pharmacology at the University of Pittsburgh and now of Columbia, Missouri. The major portion of the volume is a reprint of Guthrie's *Blood Vessel Surgery and Its Application*[3] which was originally published as a section of an international medical monograph series in 1912. This section is followed by a review covering "Fifty Years of Vascular Surgery" by Bernard Fisher, and finally, there is a short biographic sketch of Charles Guthrie.

As one reads Guthrie's report he is overwhelmed with the tremendous importance of his research observations which stemmed from work started in 1900, and he is even more impressed as he recognizes that these experiments are of greater importance today than they were when originally performed. A striking example is found in his "two-headed dog" experiment in which the head of one dog was successfully grafted to the neck of another. He clearly antedated by many years the recent Russian effort which was given a rather surprising volume of uninformed press coverage.

The first chapter of this book is a review of the early techniques of blood vessel anastomosis dating from the reports of Eck in 1879. Alexis Carrel had published a clear and simple technique of vascular anastomosis in 1902 and with his coming to this country he was associated with Guthrie in 1905 at the University of Chicago. Together, Carrel and Guthrie made great strides in improving techniques of vascular anastomoses and their technique for an end-to-side anastomosis continues as the standard procedure even today.

In these early works, they noted that blood coagulated more slowly when in contact with an oil surface and thus, the use of oiled silk sutures and paraffin-coated cannulas was devised. These same principles in the 1950's made possible the successful performance of extracorporeal circulation procedures.

The efforts of Guthrie and Carrel at brachial, cephalic, and carotid artery anastomosis led them to the successful use of autogenous vein transplants to bridge arterial defects. Other vascular substitutes were then tried which included arterial segments preserved in saline or under refrigeration and arterial homografts fixed in formaldehyde. Later, they utilized arterial heterografts from the rabbit aorta and transplanted these into the dog's brachial cephalic and carotid artery with success.

As a result of these early experiments in arterial transplantation, it was only natural that they should turn to extracorporeal perfusion of isolated organs. Their success with isolated perfusions led them to attempt biologic perfusions with techniques of cross circulation. Finally, they transplanted a dog's head into the cervical area of a second animal and function remained for more than 5 hours. Early attempts of renal, thyroid, parathyroid, ovarian, and extremity autotransplantation and homotransplantation are described as well as the effect of cardiac and cardiopulmonary homotransplantation into the dog's brachiocephalic artery.

This relatively short volume will be found well worth reading by all who are interested in cardiovascular surgery or in tissue transplantation. The bibliography is rather extensive and it will, therefore, be a valuable source for those writing in these fields. —*Thomas O. Murphy.*

THE MONOGRAPH entitled *Autolyse-Krankheiten in der Chirurgie*[4] represents a very interesting attempt to bring superficially unrelated diseases under one name. This one common denominator is intravital autolysis, and the author speaks about autolysis diseases. Such diverse conditions as heat and cold damage, lower nephron nephrosis (crush syndrome), transfusion reaction, and various allergies possess one common feature—autolysis. In the first part of the monograph these conditions are surveyed and the theoretic foundation given for each. A very exhaustive bibliography is included. The second part of the monograph is dedicated to experimental studies of the autolysis factor in experimentally simulated crush syndrome. The evidence for the dominant importance of the autolysis is quite convincing.

This monograph will be read with great interest, especially by the student of experimental medicine. —*Gunars Medins.*

THE COLLABORATIVE WORK of 18 authors, *Lokalanaesthesie und Lokalanaesthetika*[5] is meant to serve the anesthesiologist, the surgeon, and the practitioner. The text is based upon the international, including Russian, literature and the personal experiences of the authors. Modern views of the theory of pain are thoroughly presented. There is a discussion of the various groups of anesthetic agents, including their mode of action, pharmacologic effects, indication, and toxicity. Numerous pathophysiologic considerations are outlined. Illustrations are freely used for the detailed description of the technique and the hazards of an unusually large number of local and regional anesthetic procedures; these include anesthesia for abdominal and thoracic surgery. One chapter is devoted to the discussion of the therapeutic use of local anesthetic drugs. Excellent, up-to-date information is given on the theoretic and practical aspects of this subject. —*Norbert Schnelle.*

[3]THE CONTRIBUTIONS OF DR. C. C. GUTHRIE TO VASCULAR SURGERY. By Samuel P. Harbison, M.D., and Bernard Fisher, M.D. BLOOD VESSEL SURGERY AND ITS APPLICATION. By Charles Claude Guthrie, M.D., Ph.D. (A Reprint.) 83 pages, 115 illustrations. $7.50. Pittsburgh: The University of Pittsburgh Press, 1959.

[4]AUTOLYSE-KRANKHEITEN IN DER CHIRURGIE. Klinische und experimentelle Studien zur Pathogenese und Therapie einiger akuter, insbesondere posttraumatischer Krankheitsbilder. By Priv.-Doz. Dr. Leo Koslowski. Foreword by Prof. Dr. H. Krauss. 159 pages, 60 illustrations. $4.70. Stuttgart: Georg Thieme Verlag, 1959.

[5]LOKALANAESTHESIE UND LOKALANAESTHETIKA. Edited by Prof. Dr. Hans Killian. 770 pages, 341 illustrations. $36.65. Stuttgart: Georg Thieme Verlag, 1959.

THE MONOGRAPH by Professor Gellhorn, *Autonomic Imbalance and the Hypothalamus*,[6] presents the experimental basis for a method of testing the relative excitability of the sympathetic and parasympathetic centers in both experimental animals and in human beings. As an objective method for the study of problems in neuropsychiatry and medicine, it ranks with Pavlov's work on the conditioned reflex and may prove of equal value. Gellhorn states that his work had its origin in a clinical observation of Funkenstein that the intensity of the hypotensive action of mecholyl chloride showed greater variation in neuropsychiatric patients than in controls and particularly in the fact that this effect of the drug changed with the change in the mental condition of the patient. Gellhorn took this idea to the laboratory and developed it into a method for measuring the excitability of the hypothalamus in the intact organism through autonomic tests. Since the behavior of the autonomic system is much more variable than the somatic nervous system in response to a stimulus, methods for determining the state of this system should be important in both physiology and medicine.

In his experimental studies, Gellhorn uses the blood pressure and heart rate and the sympathetically innervated nictitating membrane of the cat as indicators of the tone of the autonomic system. An alteration in the balance between the sympathetic and parasympathetic systems is produced by changing the blood pressure through the action of drugs. When a hypotensive drug such as mecholyl chloride, acetylcholine, or histamine is given intravenously, the fall in the blood pressure and consequently in the sinoaortic pressure calls forth a shift in the autonomic balance to the sympathetic side. This is due to lessened discharges from the sinoaortic receptors which through their reflex action restrain the central sympathetic structures. This shift of the autonomic balance to the sympathetic side Gellhorn refers to as sympathetic tuning. The acceleration of the heart rate and the contraction of the nictitating membrane which occur as the blood pressure recovers from the drug induced hypotension indicate that in this state the central sympathetic discharges are increased. In such a state of sympathetic tuning, the autonomic system produces a greater response both to reflex and direct stimulation than under normal conditions. In a similar fashion, parasympathetic tuning is accomplished by raising the blood pressure by the injection of noradrenalin. In this state an increased responsiveness to parasympathetically acting stimuli results.

These findings call to mind the old ideas of Eppinger and Hess concerning vagotonia and sympathicotonia with the important addition, now are available objective methods of testing their validity. This monograph, beautifully printed, should be read by serious students of medicine in many fields and it is the author's hope that his work may result in the emergence of new facts and become a seedbed for new ideas. —*Lester R. Dragstedt.*

FOR THOSE seeking knowledge concerning congenital heart disease and rheumatic fever, the book *Heart Disease in Infancy and Childhood*[7] is the answer. During the past 15 years, an enormous amount of literature has been published about all phases of all types of congenital heart disease. The authors present carefully compiled reports of their own wealth of information concerning cardiac patients and to this have added the filtered and concentrated findings of others.

The book is well organized in that each chapter is developed in a similar fashion. The reader can find in an instant any particular phase of any cardiac lesion of childhood. The book contains 850 pages and many appropriate illustrations. To repeat, not only those who already are pediatric cardiologists, but especially those who are interested in becoming pediatric cardiologists, will find this book a superb guide. Even those whose interest in this subject is secondary will, when necessity demands, find clarification of diagnostic or therapeutic problems.

Every page is the result of careful work, thoughtful analysis, and clear writing. This book is recommended as a dependable guide to the problems of heart disease in children. —*Willis J. Potts.*

[6] AUTONOMIC IMBALANCE AND THE HYPOTHALAMUS: IMPLICATIONS FOR PHYSIOLOGY, MEDICINE, PSYCHOLOGY. By Ernst Gellhorn, M.D., Ph.D. 300 pages, 101 illustrations. $8.50. Minneapolis: University of Minnesota Press, 1957.

[7] HEART DISEASE IN INFANCY AND CHILDHOOD. By John D. Keith, M.D., Richard D. Rowe, M.B., (N.Z.), F.R.C.P. (Edin.), and Peter Vlad, M.D. 877 pages, illustrated. $22.50. New York: The Macmillan Co., 1958.

BOOKS RECEIVED

BOOKS received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

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MEDICAL DISCOVERIES; WHO AND WHEN. By J. E. Schmidt, M.D. 555 pages. $14.75. Springfield, Ill.: Charles C Thomas, 1959.

DISTURBANCES IN GASTROINTESTINAL MOTILITY; DIARRHEA, CONSTIPATION, BILIARY DYSFUNCTION. Edited by J. Alfred Rider, M.D., and Hugo C. Moeller, M.D. 387 pages, illustrated. $13.00. Springfield, Ill.: Charles C Thomas, 1959.

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THE SURGICAL TREATMENT OF SCOLIOSIS. By Louis A. Goldstein, M.D., F.A.C.S. Appendix, Anesthesia in Scoliosis. By D. Vernon Thomas, M.B., F.F.A.R.C.S. 116 pages, illustrated. $6.75. Springfield, Ill.: Charles C Thomas, 1959.

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PERIPHERAL FACIAL PALSY PATHOLOGY AND SURGERY. By Karsten Kettel, M.D. 341 pages, illustrated. $19.50. Springfield, Ill.: Charles C Thomas, 1959.

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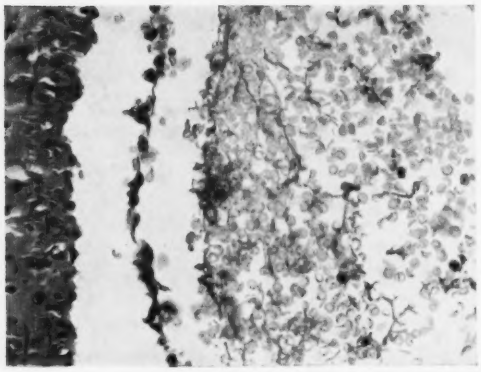

FIG. 3.

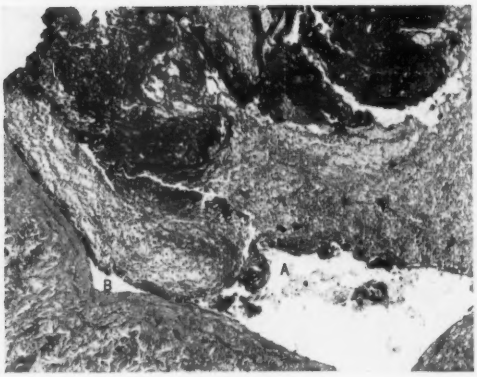

FIG. 5.

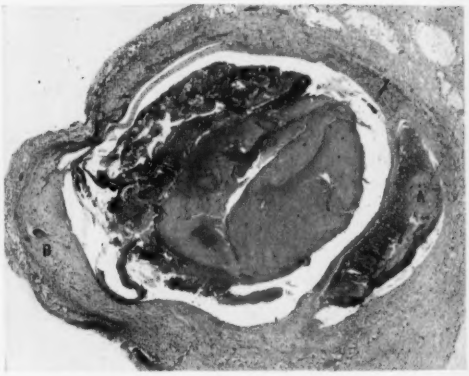

FIG. 6.

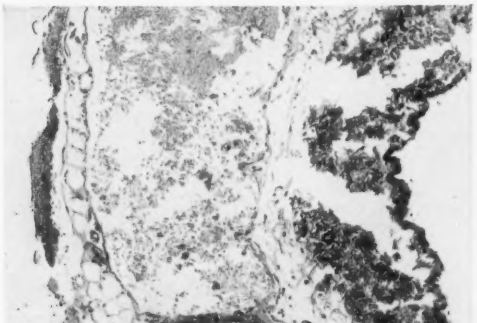

FIG. 9.

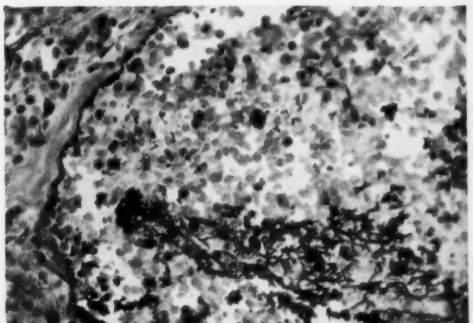

FIG. 10.

Experimental Production of Phlebothrombosis.—Hector M. Marin and Mario Stefanini.

(*Legends on opposite page.*)